REVIEW ARTICLE

*CONTINUUM* AUDIO
INTERVIEW AVAILABLE
ONLINE

# Emergent Management of Status Epilepticus

By Clio Rubinos, MD, MS

## ABSTRACT

**OBJECTIVE:** **Status epilepticus is a neurologic emergency that can be life-threatening. The key to effective management is recognition and prompt initiation of treatment. Management of status epilepticus requires a patient-specific–approach framework, consisting of four axes: (1) semiology, (2) etiology, (3) EEG correlate, and (4) age. This article provides a comprehensive overview of status epilepticus, highlighting the current treatment approaches and strategies for management and control.**

**LATEST DEVELOPMENTS:** **Administering appropriate doses of antiseizure medication in a timely manner is vital for halting seizure activity. Benzodiazepines are the first-line treatment, as demonstrated by three randomized controlled trials in the hospital and prehospital settings. Benzodiazepines can be administered through IV, intramuscular, rectal, or intranasal routes. If seizures persist, second-line treatments such as phenytoin and fosphenytoin, valproate, or levetiracetam are warranted. The recently published Established Status Epilepticus Treatment Trial found that all three of these drugs are similarly effective in achieving seizure cessation in approximately half of patients. For cases of refractory and super-refractory status epilepticus, IV anesthetics, including ketamine and γ-aminobutyric acid–mediated (GABA-ergic) medications, are necessary. There is an increasing body of evidence supporting the use of ketamine, not only in the early phases of stage 3 status epilepticus but also as a second-line treatment option.**

**ESSENTIAL POINTS:** **As with other neurologic emergencies, "time is brain" when treating status epilepticus. Antiseizure medication should be initiated quickly to achieve seizure cessation. There is a need to explore newer generations of antiseizure medications and nonpharmacologic modalities to treat status epilepticus.**

**CITE AS:**
CONTINUUM (MINNEAP MINN)
2024;30(3, NEUROCRITICAL CARE):
682–720.

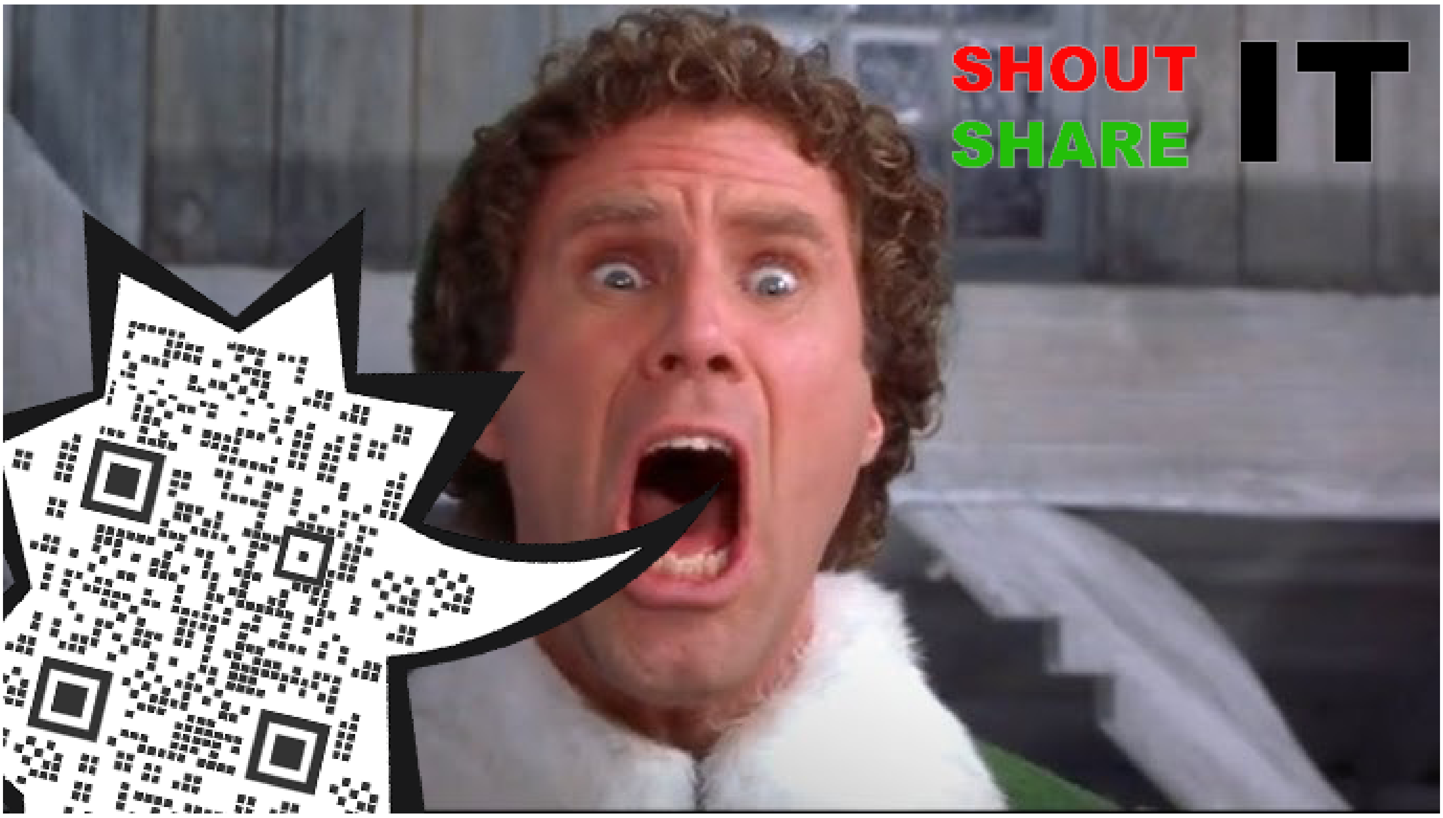
Address correspondence to
Dr Clio Rubinos, 170 Manning
Dr, Physician Office, CB 7025,
Chapel Hill, NC 27599-7025,
crubinos@unc.edu.

**RELATIONSHIP DISCLOSURE:**
Dr Rubinos has received personal compensation in the range of $500 to $4999 for serving as a consultant for Qualtrics, for serving on a scientific advisory or data safety monitoring board for Azurity Pharmaceuticals, Inc, and for serving on a speakers bureau for the American Epilepsy Society and in the range of $5000 to $9999 for serving on a speakers bureau for Marinus Pharmaceuticals, Inc. The institution of Dr Rubinos has received research support from the University of North Carolina.

**UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:**
Dr Rubinos reports no disclosure.

## INTRODUCTION

Status epilepticus is a neurologic emergency associated with significant morbidity and mortality that increases as seizures become more refractory to medical therapy.[1] Seizures result from the paroxysmal, hypersynchronous, abnormal activity of neurons in the cerebral cortex. Seizures are typically self-limited, lasting less than 5 minutes. When seizures extend beyond this timeframe, they often do not resolve on their own. In the past, status epilepticus was commonly defined as either continuous


SHOUT
SHARE
IT

seizure activity or the occurrence of two or more seizures without the recovery of consciousness lasting beyond a duration of 30 minutes. However, in 2015, a new operational definition was introduced to define status epilepticus. This definition of status epilepticus establishes two time points: T1 (5 or 10 minutes for convulsive or focal status epilepticus, respectively) and T2 (30 minutes or 60 minutes for convulsive or focal status epilepticus, respectively). This operational definition follows the International League Against and the Commission on Epidemiology proposal of status epilepticus as continuous seizure activity:

> *Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.*[2]

The time point referred to as T1 signifies the moment when seizures typically do not cease spontaneously. Treatment should be initiated at this stage, which is at 5 minutes for bilateral tonic-clonic (ie, convulsive) status epilepticus and at 10 minutes for focal status epilepticus, with or without impairment of consciousness. The time point known as T2 represents the moment when neuronal damage and long-term consequences may occur. It serves as a crucial indicator that status epilepticus should be brought under control by this time, with a maximum of 30 minutes for bilateral tonic-clonic status epilepticus (FIGURE 6-1).[2] This operational definition was created to pragmatically emphasize therapy because treatment should be started emergently and should not be delayed until the T2 time when neuronal injury has started, and the development of pharmacoresistance has arisen.

**KEY POINTS**

- **The most updated definition of status epilepticus establishes two time points: T1 (5 or 10 minutes for convulsive or focal status epilepticus, respectively) and T2 (30 or 60 minutes for convulsive or focal status epilepticus, respectively).**
- **At time T1 of status epilepticus, seizures typically do not cease spontaneously, and treatment should be started immediately.**
- **At time T2 of status epilepticus, neuronal damage, and long-term consequences may occur, hence seizure termination before T2 is critical.**
- **Status epilepticus progresses in four stages: (1) early or impending status epilepticus (stage 1), (2) established (stage 2), (3) refractory (stage 3), and (4) super-refractory status epilepticus (stage 4).**
- **Prolonged refractory status epilepticus is a subcategory of refractory status epilepticus (stage 3) that persists for at least 7 days despite appropriate management but without the use of aesthetics.**

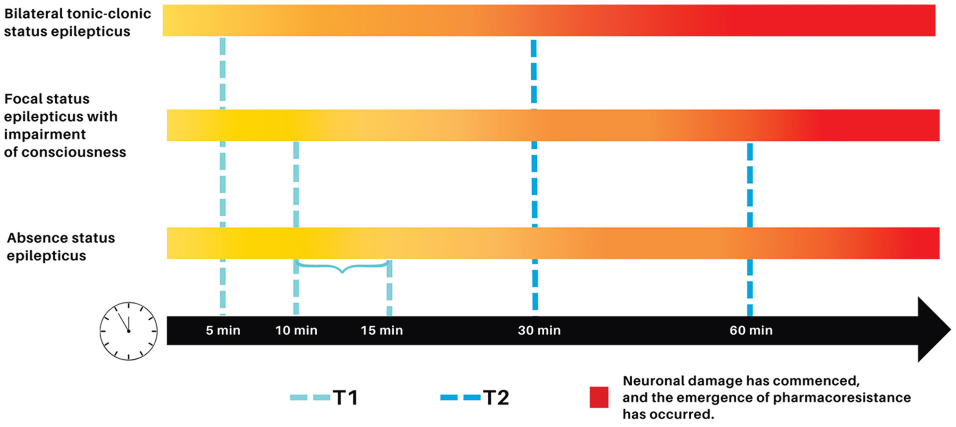

Bilateral tonic-clonic status epilepticus
Focal status epilepticus with impairment of consciousness
Absence status epilepticus
5 min
10 min
15 min
30 min
60 min
T1
T2
Neuronal damage has commenced, and the emergence of pharmacoresistance has occurred.

**FIGURE 6-1**

**Operational dimensions of status epilepticus. T1 represents the point at which emergency treatment for status epilepticus should be initiated, and T2 indicates the timeframe in which long-term consequences may arise. At T1, seizures have the potential to become prolonged, leading to continuous seizure activity. At T2, seizures may result in long-term consequences, such as neuronal injury, neuronal death, neuronal networks rearrangement, and functional deficits.**

There are four progressive stages of status epilepticus (FIGURE 6-2): (1) early or impending status epilepticus (ie, stage 1), (2) established (ie, stage 2), (3) refractory (ie, stage 3) and (4) super-refractory status epilepticus (ie, stage 4).[3] Impending status epilepticus (stage 1) is defined as continuous or intermittent seizures lasting more than 5 min, without full recovery of consciousness between seizures.[4] Established status epilepticus (stage 2) develops 10 to 30 minutes after seizure onset in patients who do not respond to benzodiazepines.[5] Refractory status epilepticus (stage 3) denotes either clinical or electrographic seizures that persist after the administration of two antiseizure medications, the first being an adequate dose of an initial benzodiazepine.[6] Super-refractory status epilepticus (stage 4) is defined as status epilepticus that continues for at least 24 hours after the initiation of anesthesia, either without interruption despite appropriate status epilepticus anesthesia doses, reoccurrence during appropriate status epilepticus anesthetic doses administration, or reoccurrence after the withdrawal of anesthesia, necessitating anesthetic reintroduction.[7] There is a subcategory of stage 3 and stage 4 for patients with prolonged status epilepticus:[8]

- **Prolonged refractory status epilepticus: refractory status epilepticus that persists for at least 7 days despite appropriate management but without the use of anesthetics.**

- **Prolonged super-refractory status epilepticus: super-refractory status epilepticus that persists for at least 7 days, including ongoing need for anesthetics.**

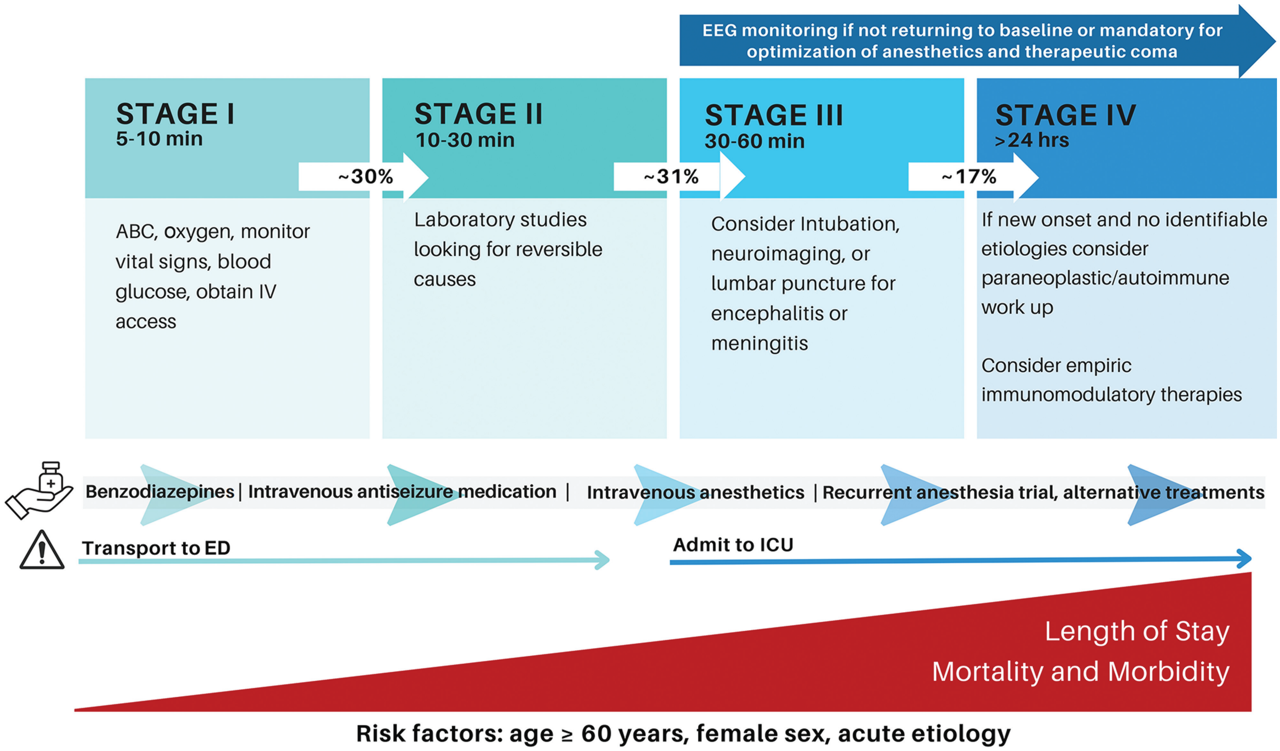

EEG monitoring if not returning to baseline or mandatory for optimization of anesthetics and therapeutic coma
STAGE I
5-10 min
~30%
STAGE II
10-30 min
~31%
STAGE III
30-60 min
~17%
STAGE IV
>24 hrs
ABC, oxygen, monitor vital signs, blood glucose, obtain IV access
Laboratory studies looking for reversible causes
Consider Intubation, neuroimaging, or lumbar puncture for encephalitis or meningitis
If new onset and no identifiable etiologies consider paraneoplastic/autoimmune work up
Consider empiric immunomodulatory therapies
Benzodiazepines | Intravenous antiseizure medication | Intravenous anesthetics | Recurrent anesthesia trial, alternative treatments
Transport to ED
Admit to ICU
Length of Stay
Mortality and Morbidity
Risk factors: age ≥ 60 years, female sex, acute etiology

FIGURE 6-2
**Clinical course and treatment stages of status epilepticus.**
ABC = airway, breathing, circulation; ED = emergency department; ICU = intensive care unit.

Although these latter terms may not be widely used within the medical community, it is clinically important to acknowledge them because they may have distinct prognostic implications. A subtype of refractory status epilepticus is new-onset refractory status epilepticus (NORSE). This term describes a clinical presentation observed in patients with newly developed refractory status epilepticus who do not have any relevant preexisting neurologic disorders, including active epilepsy, and do not exhibit any clear acute or active structural, metabolic, or toxic causes.[8] NORSE does not specify any particular cause of status epilepticus. A subcategory of NORSE is called febrile infection-related epilepsy syndrome (FIRES). FIRES can occur at any age and is characterized by a preceding febrile infection that starts between 2 weeks and 24 hours before the onset of refractory status epilepticus, but the presence of fever before the onset of status epilepticus is not exclusive to FIRES.[8] With this definitional background, we turn now to a discussion of the pathophysiology, epidemiology, classification, evaluation and diagnosis, management, and outcome of status epilepticus.

## PATHOPHYSIOLOGY

Following seizure onset, a cascade of events takes place. Within milliseconds to seconds, neurotransmitters are released, ion channels open and close, and protein phosphorylation occurs, all of which collectively contribute to the development of potentially prolonged seizures. These events are followed within seconds to minutes by receptor trafficking, leading to an increase in the number of physiologically active excitatory α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. As a result, there is an increase in intracellular calcium mediated by glutamate, which can cause heightened excitation, apoptosis, and mitochondrial dysfunction. Concurrently, synaptic inhibitory γ-aminobutyric acid A ($GABA_A$) β2, β3, and γ2 subunits are reduced as they are internalized by endocytosis. This reduction in GABA receptors hampers the effectiveness of GABA agonist medications, such as benzodiazepines and barbiturates, contributing to the refractoriness of seizures.[9] Further, over minutes to hours, changes in neuropeptide expression occur, characterized by an augmentation in excitatory substance P and insufficient levels of inhibitory neuropeptide Y, perpetuating an excitatory state and maintaining hyperexcitability contributing to pharmacoresistance. In the days to weeks following status epilepticus, genetic and epigenetic modifications transpire, leading to alterations in the expression of multiple genes. Additionally, there may be changes in microRNA regulation and DNA methylation, which cause neuronal network reorganization, epileptogenesis, and further neuronal damage.[9] Downregulation of synaptic GABA receptors happens within minutes after uncontrolled status epilepticus, causing resistance to benzodiazepines. Time is brain in status epilepticus, and treatment should be started emergently.

## EPIDEMIOLOGY

The incidence of status epilepticus ranges from 18.3 to 41 per 100,000 people per year in the United States and 10 to 16 per 100,000 people per year in Europe.[9,10] Less is known about the epidemiology of status epilepticus in developing countries. Although studies are limited, the incidence of status epilepticus in Latin America is estimated to be approximately 24.3 per 100,000 people per year,[11] in Africa the incidence in children is approximately 35 per 100,000 people per year,[12] and in Asia it ranges between 4.6 and 5.5 per 100,000 people per

### KEY POINTS

- **Prolonged super-refractory status epilepticus is a subcategory of super-refractory status epilepticus (stage 4) that persists for at least 7 days, including the ongoing need for anesthetics.**
- **Downregulation of γ-aminobutyric acid (GABA) receptors happens within minutes after uncontrolled status epilepticus, causing resistance to benzodiazepines.**
- **Status epilepticus is a common neurologic emergency, also seen in critically ill patients and in all intensive care units.**
- **The International League Against Epilepsy classifies status epilepticus using four axes: (1) semiology, (2) etiology, (3) EEG correlates, and (4) patient age.**
- **It is crucial to consider and address each relevant axis to determine the etiology of status epilepticus and prevent the recurrence of seizures.**

year.[13] However, the incidence of status epilepticus in low- and middle-income countries might be underreported because of the absence of electroclinical data necessary for diagnosing nonconvulsive status epilepticus.

There is scarce literature about the incidence of refractory status epilepticus and super-refractory status epilepticus in the United States. However, it is estimated that the incidence of super-refractory status epilepticus is 13 per 100,000 people per year.[10] In Europe, the estimated incidence of refractory status epilepticus ranges from 3 to 7.2 cases per 100,000 people per year, whereas the incidence of super-refractory status epilepticus is lower, ranging from 0.6 to 1.2 cases per 100,000 people per year.[14–17] Notably, epidemiology data about status epilepticus are impacted by various factors, including age, the methodology used to identify cases, and the duration criteria for defining status epilepticus (such as 5 minutes, 10 minutes, or 30 minutes).

Status epilepticus incidence has a bimodal age distribution, with the first peak in the early years of life (ie, younger than 10 years) and the second peak after the age of 50 years.[18] Data from Europe demonstrate that in children, there is an estimated incidence of 17.6 cases of status epilepticus per 100,000 children per year, 3.9 cases of refractory status epilepticus per 100,000 children per year, and 2.3 cases of super-refractory status epilepticus per 100,000 children per year.[19] A 2019 population-based study from Austria reported an age- and sex-adjusted annual incidence rate of 79.9 cases (95% confidence interval [CI], 53.4 to 114.8) per 100,000 older adults (ie, aged 60 years or older). The annual incidence rate was 89.6 (95% CI, 54.0 to 139.7) in older women and 67.6 (95% CI, 32.3 to 124.7) in older men.[14]

Status epilepticus, which can have prominent motor features or be nonconvulsive, is a common complication in critically ill patients.[20] The predominant seizure type that involves prominent motor symptoms is generalized convulsive seizures (90%). More than 50% of patients with generalized convulsive status epilepticus have acute brain injuries (eg, ischemic or hemorrhagic stroke, traumatic brain injury, or hypoxic-ischemic brain injury) or acute systemic changes (eg, hypoglycemia, drug intoxication and withdrawal, or systemic infections).[21] Nonconvulsive status epilepticus is the most common type of status epilepticus in all intensive care units (ICUs); in fact, nonconvulsive status epilepticus occurs in 5% to 20% of patients who are comatose in non-neurologic ICUs.[22,23]

Heterogeneous definitions of status epilepticus have been a barrier to understanding the epidemiology of nonconvulsive status epilepticus, particularly because of the exponential growth of continuous EEG monitoring in critically ill patients.[24] Although some data suggest the incidence of nonconvulsive status epilepticus is 10 to 20 cases per 100,000 people per year,[25,26] nonconvulsive status epilepticus accounts for approximately 21% to 47% of cases of status epilepticus in the ICU.[25,26] Patients with convulsive status epilepticus before the initiation of continuous EEG monitoring are at the highest risk for nonconvulsive status epilepticus; 33% to 46% of patients with convulsive status epilepticus progress to nonconvulsive status epilepticus.[22,27] Among critically ill patients with generalized convulsive status epilepticus, 38% to 50% develop nonconvulsive status epilepticus.[25,26] Additionally, critically ill patients with nonconvulsive status epilepticus may present with altered mental status; 8% to 48% of critically ill adults and 6% to 47% of critically ill children with altered mental status in the medical or surgical ICU have nonconvulsive status epilepticus.[22,28,29] Critically ill patients are particularly at risk for nonconvulsive status epilepticus if they have acute brain injuries; nonconvulsive status epilepticus occurs in 43% of critically ill patients with encephalitis, 20% of patients with subarachnoid hemorrhage, 18% of patients with intracerebral hemorrhage, and 15% of patients with ischemic stroke.[28,30–33] Of patients with nonconvulsive status epilepticus, 20% to 31% progress to refractory status epilepticus,[16,34] and 11% to 17% have recurrent seizures after withdrawal of anesthetics (super-refractory status epilepticus).[34,35]

## CLASSIFICATION

The International League Against Epilepsy classifies status epilepticus using four axes: (1) semiology, (2) etiology, (3) EEG correlates, and (4) patient age. The International League Against Epilepsy axis 1, semiology, broadly categorizes status epilepticus with prominent motor phenomena (ie, convulsive status epilepticus) and status epilepticus without prominent motor phenomena (ie, nonconvulsive status epilepticus) (**FIGURE 6-3**). However, the clinical symptomatology of status epilepticus can change and evolve throughout its course, commonly referred to as the *evolution of semiology*, and this can impact outcome.[14] The second axis addresses the underlying etiology of status epilepticus, divided into two main categories: (1) known and (2) unknown (ie, cryptogenic). Known etiologies can have varying temporal relationships with the onset of status epilepticus: acute (eg, encephalitis, traumatic brain injury, stroke), remote (eg, postencephalitis, posttraumatic, poststroke), or progressive

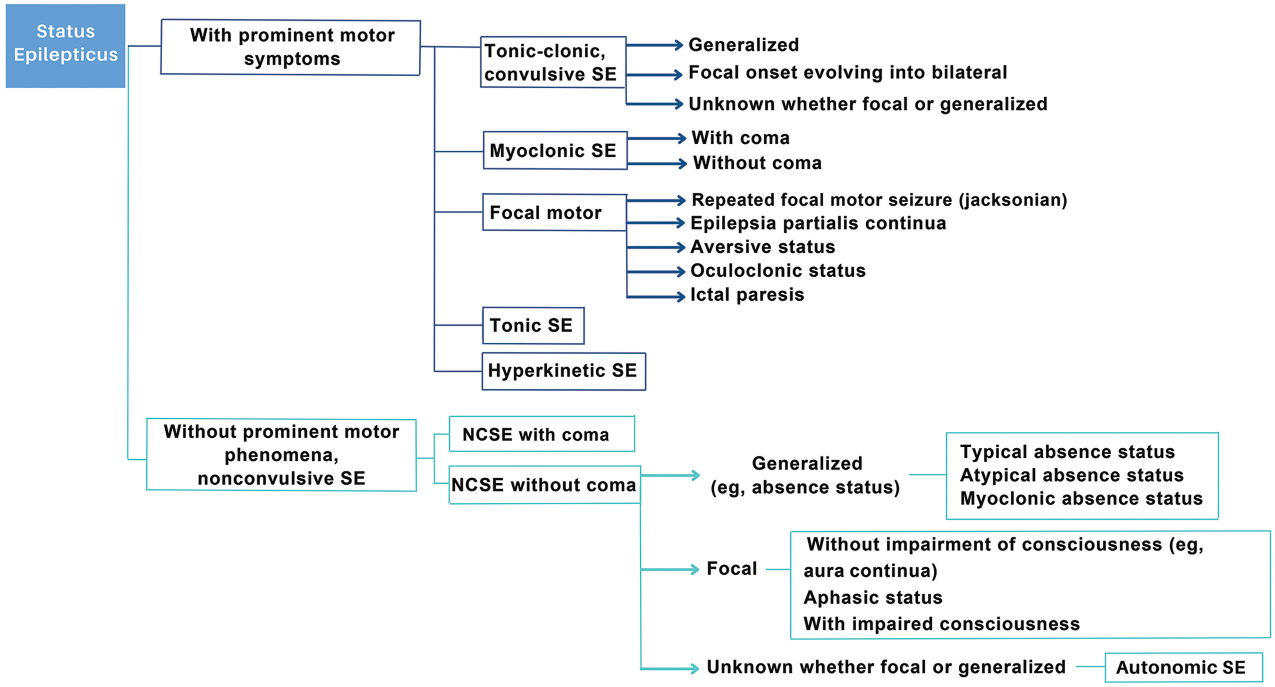

Status Epilepticus
With prominent motor symptoms
Tonic-clonic, convulsive SE
Generalized
Focal onset evolving into bilateral
Unknown whether focal or generalized
Myoclonic SE
With coma
Without coma
Focal motor
Repeated focal motor seizure (jacksonian)
Epilepsia partialis continua
Aversive status
Oculoclonic status
Ictal paresis
Tonic SE
Hyperkinetic SE
Without prominent motor phenomena, nonconvulsive SE
NCSE with coma
NCSE without coma
Generalized (eg, absence status)
Typical absence status
Atypical absence status
Myoclonic absence status
Focal
Without impairment of consciousness (eg, aura continua)
Aphasic status
With impaired consciousness
Unknown whether focal or generalized
Autonomic SE

**FIGURE 6-3**

**Classification scheme for status epilepticus proposed by the International League Against Epilepsy Task Force on classification of status epilepticus.**

EPC = epilepsia partialis continua; NCSE = nonconvulsive status epilepticus; SE = status epilepticus.
Data from Trinka E, et al, Seizure.[2]

(eg, dementia, tumors). The third axis, the EEG correlate, is determined by describing the EEG pattern using various parameters, including location, pattern name, morphology, time-related features, modulation, and the impact of interventions, such as medication, on the EEG tracing (TABLE 6-1). The fourth axis, age, denotes that certain syndromes consist of a combination of electrographic and semiologic seizure types that commonly emerge at specific ages and frequently exhibit distinctive responses to particular antiseizure medications or are triggered by specific factors. It is crucial to consider and address each relevant axis to determine the etiology of status epilepticus and prevent the recurrence of seizures. The establishment of the International League Against Epilepsy's operational definition of status epilepticus and the identification of these four axes, which are explored further in this article, marks a crucial milestone in the standardization of diagnostic procedures and approaches to status epilepticus.

## Semiology

Axis 1, semiology, classifies status epilepticus based on clinical presentation (FIGURE 6-3) to distinguish between convulsive status epilepticus and nonconvulsive status epilepticus. Patients with convulsive status epilepticus present with varying motor manifestations according to seizure type. Clinical manifestations of generalized convulsive status epilepticus are ceaseless generalized tonic-clonic activity with impaired consciousness or a succession of generalized tonic-clonic activities, without return to consciousness in between seizures. Myoclonic status epilepticus is characterized by frequent, generalized, or focal myoclonic jerks that can be rhythmic or arrhythmic. Myoclonic jerks are brief, involuntary muscle contractions that can affect one or multiple muscles

TABLE 6-1

### EEG Considerations in Status Epilepticus[a]

**Location**

◆ Generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal

**Name of the pattern**

◆ Periodic discharges, rhythmic delta activity or spike-and-wave and sharp-and-wave plus subtypes

**Morphology**

◆ Sharpness, number of phases (eg, triphasic morphology), absolute and relative amplitude, polarity

**Time-related features**

◆ Prevalence, frequency, duration, daily pattern duration and index, onset (eg, sudden versus gradual), dynamics (eg, evolving, fluctuating, or static)

**Modulation**

◆ Stimulus-induced versus spontaneous

**Effect of intervention on the EEG**

◆ Degree and durability of response to antiseizure interventions and can be symmetric or asymmetric. Tonic status epilepticus consists of the maintenance of a tonic posture and usually occurs in children, particularly with diagnosed syndromic epilepsy, such as Lennox-Gastaut syndrome. Focal motor status epilepticus has many clinical manifestations, and they depend on the area of the cortex where symptoms and clinical signs originate, but they also can progress along the homunculus (jacksonian march) with or without consciousness impairment. Refractory focal motor status epilepticus with prolonged and regular jerking activity with retained awareness is called epilepsia partialis continua.[36] Epilepsia partialis continua can be remarkably persistent, with jerks that tend to be stereotyped, affecting single muscle groups, entire limbs, or larger parts of the hemibody for days, weeks, or even decades.[36]

---

[a] Data from Trinka E, et al, Epilepsia.[2]

Axis 1 is defined by clinical presentation. There are two major subtypes: (1) with prominent motor phenomena and (2) without prominent motor phenomena. Instead of motor phenomena, patients with nonconvulsive status epilepticus have impairment of consciousness ranging from mild confusion to

**Subtle Clinical Symptoms in Nonconvulsive Status Epilepticus** **TABLE 6-2**

**Negative symptoms**

- Mutism and aphasia
- Amnesia and intermittent cognitive impairment
- Anorexia
- Coma
- Lethargy
- Stupor
- Personality changes
- Confusion
- Behavioral arrest and staring
- Asystole

**Positive symptoms**

- Agitation and aggression
- Delirium
- Hallucinations
- Echolalia
- Nystagmus and hippus
- Facial, oral, ocular twitching
- Bradyarrhythmia and tachyarrhythmia
- Psychosis
- Perseveration
- Laughter
- Crying
- Nausea and emesis

**TABLE 6-3**

### List of Potential Etiologies for Status Epilepticus[a]

**Antiseizure medications**

- Medication interaction reducing effectiveness
- Nonadherence to medications

**Autoimmune disorders**

- α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor encephalitis
- Anti–β1 subunit of the γ-aminobutyric acid B ($\text{GABA}_\text{B}$) receptor encephalitis
- Anti–leucine-rich glioma inactivated (LGI) protein 1 encephalitis
- Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis
- Antibody-negative limbic encephalitis
- Hashimoto encephalitis
- Lupus vasculitis
- Multiple sclerosis
- Paraneoplastic encephalitis
- Voltage-gated potassium channel receptor encephalitis

**Genetic diseases**

- Angelman syndrome
- Down syndrome (trisomy 21)
- Fragile X syndrome
- Rett syndrome
- Ring chromosome 17
- Ring chromosome 20
- Wolf-Hirschhorn syndrome
- X-linked mental disability syndrome

**Infectious diseases**

- Bacterial meningitis
- Human immunodeficiency virus (HIV)
- Progressive multifocal leukoencephalopathy
- Neurocysticercosis
- Prion diseases (Creutzfeldt-Jakob disease)
- Toxoplasmosis
- Tuberculosis
- Viral encephalitis

CONTINUED ON PAGE 691

CONTINUED FROM PAGE 690

**Metabolic abnormalities**

- Hypocalcemia
- Hypoglycemia or hyperglycemia
- Hyponatremia
- Hypomagnesemia
- Liver failure
- Sepsis
- Uremia

**Mitochondrial diseases**

- Alpers disease
- Leigh syndrome
- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia, and retinitis pigmentosa (NARP)

**Progressive diseases**

- Neurodegenerative disease (Alzheimer disease, corticobasal degeneration, frontotemporal dementia)
- Sturge-Weber syndrome
- Tuberous sclerosis

**Structural diseases (acute)**

- Cerebrovascular diseases
- Hypoxic-ischemic brain injury
- Traumatic brain injury
- Tumors

**Structural diseases (chronic and remote)**

- Cortical malformations
- History of brain injury (cerebrovascular disease, traumatic brain injury)
- History of neurosurgical intervention
- Perinatal cerebral ischemia
- Tumors

**Toxins**

- Alcohol intoxication
- Drugs
- Heavy metals

CONTINUED ON PAGE 692

CONTINUED FROM PAGE 691

- **Medications that lower seizure threshold**
  - Theophylline
  - Carbapenems
  - Cefepime
  - Quinolone antibiotics
  - Isoniazid
  - Tricyclic antidepressants
  - Bupropion
- **Lithium**

**Withdrawal**

- **Alcohol**
- **Baclofen**
- **Barbiturates**
- **Benzodiazepines**

---

[a] Data from Trinka E, et al, Epilepsia.[37]

coma. However, subtle clinical features can be seen, and these can be categorized into two groups: (1) negative symptoms or (2) positive symptoms (**TABLE 6-2**).

### Etiology

There are multiple possible etiologies for status epilepticus (**TABLE 6-3**[37]), which differ according to overall condition (eg, critically ill versus ambulatory) and geographic location (eg, lower- and middle-income countries versus higher-income countries). The etiology of status epilepticus can be divided into the following categories: known or symptomatic and unknown or cryptogenic. In general, there are five groups of known etiologies of status epilepticus: (1) structural, (2) metabolic, (3) inflammatory, (4) infectious, or (5) toxic. In critically ill patients, the most common cause of status epilepticus is an underlying structural or nonstructural brain injury, which can be divided into the following categories: acute symptomatic, remote symptomatic, and progressive symptomatic.[2] If status epilepticus occurs within 1 week of a structural brain injury or within 24 hours of a severe metabolic derangement, it is referred to as *provoked or acute symptomatic status epilepticus*.

In ambulatory patients, the most common causes of status epilepticus are epileptic syndromes, generally in the setting of changes in antiseizure medications, medication nonadherence, or medication interactions that lower antiseizure medication levels, and remote symptomatic etiologies such as stroke.[37] Acute symptomatic causes represent the most prevalent etiology, accounting for approximately 48% to 63% of all cases of status epilepticus. An international online questionnaire revealed distinct etiologies of status epilepticus based on geographic location.[38] In Asia, the most commonly reported etiology was infection, particularly acute encephalitis. Vascular etiologies were more prevalent in Europe compared with Asia. However, trauma was equally reported in the Americas, Europe, and Asia. Unfortunately, because of the small number of patients from Africa included in the study (n = 9), subgroup analyses could not be conducted for the African continent. There are limited epidemiologic studies on status epilepticus in Africa. However, Sadarangani and colleagues[12] found that infection was the most common cause of status epilepticus in children in Africa. Among these causes, malaria without febrile convulsion was identified as the primary etiology, followed by febrile convulsion secondary to malaria. Indeed, the high incidence of status epilepticus in low- and middle-income countries stems from the significant prevalence of patients with preventable factors such as neurologic infections.[39] The available data emphasize the existence of regional variations in the underlying causes of status epilepticus across different continents.

Although the common causes of status epilepticus can generally be identified within the initial hours of presentation, uncommon or rare causes require a comprehensive evaluation to initiate appropriate treatment. It is wise to adopt a consistent approach to the diagnostic workup of status epilepticus to evaluate for structural, metabolic, inflammatory, infectious, or toxic etiologies to ensure prompt initiation of appropriate interventions. If this comprehensive workup is unrevealing within 72 hours of seizure onset, it is necessary to consider autoimmune etiologies of status epilepticus, particularly in cases of NORSE, as illustrated in CASE 6-1.

### Electroencephalography

Electroencephalography (axis 3) is crucial in diagnosing status epilepticus, particularly in cases of nonconvulsive status epilepticus in which the clinical symptoms are subtle or unclear. The increased use of continuous EEG monitoring for the detection of nonconvulsive status epilepticus[24] has led to the detection of a variety of potentially harmful epileptiform abnormalities, particularly in patients who are comatose or critically ill.[40] TABLE 6-4 delineates patterns on the ictal-interictal continuum (eg, rhythmic or periodic EEG patterns with features concerning for ongoing electrographic seizures but not meeting formal electrographic criteria to be definitely characterized as ictal).[41] FIGURE 6-5 presents a synopsis of the 2021 American Clinical Neurophysiology Society EEG terminology.[41]

### Age

The fourth axis, age, emphasizes that certain types of status epilepticus are more common in particular age groups. The predefined age ranges to characterize status epilepticus are neonatal (0 to 30 days), infancy (1 month to 2 years), childhood (older than 2 years to 12 years), adolescence and adulthood (older than 12 years to 59 years), and older age (60 years and older). Age is important to define some electroclinical syndromes or triggers that precipitate status epilepticus.

## EVALUATION AND DIAGNOSIS OF STATUS EPILEPTICUS

The evaluation and diagnosis of status epilepticus relies on the prompt recognition of the clinical scenario, including semiology and patient risk factors and demographics. EEG may confirm convulsive status epilepticus, but EEG is essential for detecting nonconvulsive status epilepticus.

### Convulsive Status Epilepticus

Convulsive status epilepticus is a clinical diagnosis. The evaluation of convulsive status epilepticus involves a clinical assessment, laboratory tests, imaging

**KEY POINTS**

- **Axis 1 of status epilepticus classification, semiology, is based on the clinical presentation. There are two major subtypes: (1) with prominent motor phenomena and (2) without prominent motor phenomena.**

- **Axis 2 of status epilepticus classification, etiology, is divided into symptomatic (ie, acute symptomatic, remote symptomatic, and progressive symptomatic) and cryptogenic etiologies.**

- **Axis 3 of status epilepticus classification, EEG correlates, can show clear ictal activity or repetitive or periodic patterns, including the ictal-interictal continuum.**

- **Axis 4 of status epilepticus classification, age, is important to define some electroclinical syndromes or triggers precipitating status epilepticus. It can be divided into neonatal (0 to 30 days), infancy (1 month to 2 years), childhood (older than 2 years to 12 years), adolescence and adulthood (older than 12 years to 59 years), and older age (60 years and older).**

## CASE 6-1

A 38-year-old woman presented with 3 days of altered mental status and episodes of hyperventilation. Her past medical history was unremarkable. She was intubated for airway protection. Comprehensive laboratory blood tests including a complete blood cell count with differential, comprehensive metabolic panel, magnesium, phosphorus, toxicology screen, and urine analysis were unremarkable. CT and MRI of her brain were unremarkable. CSF studies showed mild pleocytosis with normal glucose and protein. Serum anti–thyroid peroxidase antibodies, human immunodeficiency virus (HIV), and viral CSF studies were negative. Whole-body CT scan and fludeoxyglucose positron emission tomography (FDG-PET) did not reveal any malignancy. Onconeuronal antibodies and those against cell surface antigens (*N*-methyl-D-aspartate [NMDA] receptor, anti–leucine-rich glioma inactivated [LGI] protein 1, contactin-associated proteinlike [CASPR] 2, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptor, γ-aminobutyric acid A [$GABA_A$] receptor, and $GABA_B$ receptor) were negative, but anti-glutamic acid decarboxylase 65 (GAD65) antibodies were positive (results were received on day 10 of her hospitalization).

The EEG performed emergently at presentation showed continuous 3-Hz to 4-Hz generalized periodic discharges, compatible with electrographic status epilepticus (FIGURE 6-4A). She had no motor manifestation. She was given 4 mg of lorazepam then loaded with 3.6 g (60 mg/kg) of levetiracetam and 400 mg of lacosamide and started on midazolam, which was titrated up to 1.6 mg/kg/h, and propofol at 60 µg/kg/min. To achieve seizure suppression, ketamine infusion was added and titrated up to 4 mg/kg/h, and propofol was discontinued. Simultaneously, she was loaded with IV fosphenytoin (20 mg/kg for a total of 1.2 g) and zonisamide (600 mg divided in two doses given 6 hours apart). Seizures persisted, so all infusions were stopped because of lack of therapeutic benefit, and pentobarbital was started at 1 mg/kg/h after a 5 mg/kg bolus. Given the refractoriness of her seizures and the suspicion of autoimmune encephalitis even before antibody results were reported, she was started on empiric methylprednisolone on day 2 of her hospitalization.

After 48 hours of suppression (FIGURE 6-4B), pentobarbital was weaned, but there was a recurrence of generalized periodic discharges that at times increased in frequency up to 3 Hz (FIGURE 6-4C), during which she had head bobbing, compatible with electroclinical seizures. Pentobarbital was restarted for a second 48 hours of suppression, and she was started on a ketogenic diet, but this was discontinued because of lack of efficacy, and she was given intravenous immunoglobulin (IVIg). After the second trial of background suppression, seizures were controlled without recurrence upon weaning pentobarbital. A tracheostomy and percutaneous endoscopy gastrostomy tube were placed. After 4 months of hospitalization, she was discharged to an acute rehabilitation facility. She was awake, alert, conversant, and following commands in all extremities.

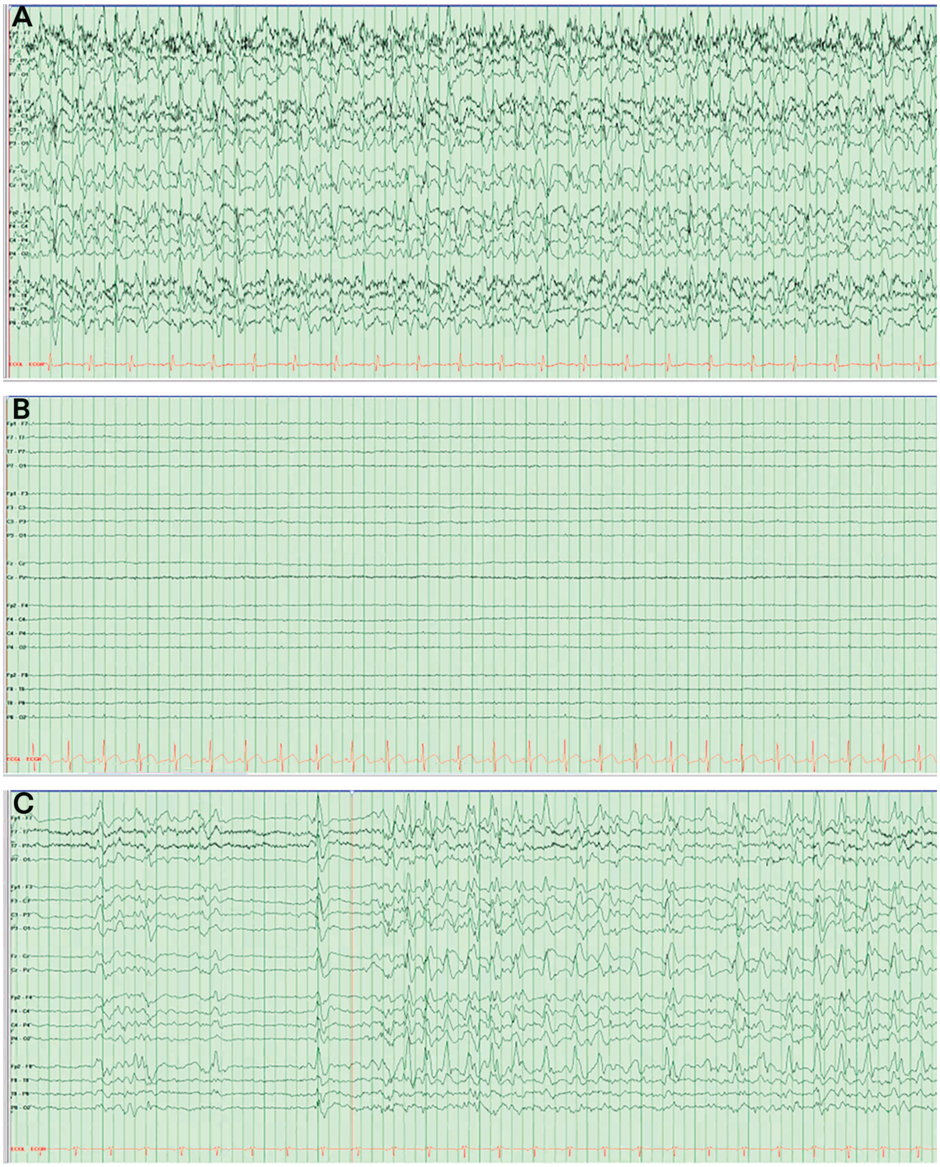


**FIGURE 6-4**

**EEG findings for the patient in CASE 6-1. *A,* Continuous 3- to 4-Hz generalized periodic discharges. *B*, Suppressed EEG. *C*, Generalized periodic discharges. These EEGs have a sensitivity of 7 μV/mm and a time base of 30 mm/s.**

**COMMENT**

This case demonstrates the progression of nonconvulsive status epilepticus to super-refractory motor status epilepticus. When there is a strong suspicion of an autoimmune cause for status epilepticus, it is advisable to consider immunotherapy even before antibody results are available. Additionally, this case underscores the significance of patience and persistence in managing autoimmune refractory status epilepticus because patients can ultimately achieve favorable outcomes despite a prolonged and challenging clinical course.

studies, and, in some cases, electroencephalography (when there is no recovery of consciousness). The initial assessment involves evaluating the patient's level of consciousness, airway, breathing, circulation, disability, and exposure. All patients should have continuous monitoring of their vital signs, especially oxygen saturation, because of the suppression of the gag reflex during convulsive status epilepticus and risk of aspiration. Patients should be given 100% oxygen during and after a seizure as they may become hypoxic because of the potential for inadequate ventilation or apnea, inability to protect the airway, or refractory hypoxemia. Clinicians should be prepared to use bag-mask ventilation and intubate. Initial blood studies should include serum glucose, complete metabolic panel (including phosphorus and magnesium), complete blood count, urine and blood toxicology, serum antiseizure medication levels (if applicable), and pregnancy tests in patients with childbearing potential. Additionally, consider ordering troponin and pyridoxine levels. Patients with status epilepticus may have myocardial ischemia or postictal neurogenic stunned myocardium caused by vascular lesions or by a mismatch of oxygen supply and demand in the myocardium.[42,43] Pyridoxine deficiency is common in patients presenting with status epilepticus, especially in those who are refractory to benzodiazepines.[44] If there is suspicion of a central nervous system inflammatory or infectious cause of status epilepticus, a lumbar puncture should be performed.

Neuroimaging is helpful in determining the cause of status epilepticus. A CT scan of the head is indicated urgently in patients for whom the etiology of status epilepticus is unknown once convulsions have been controlled. However, MRI provides a higher diagnostic yield in determining the underlying cause of status epilepticus. MRI can also reveal abnormalities caused by prolonged seizures themselves, which are often reversible. These abnormalities can be observed as areas of increased signal intensity on fluid-attenuated inversion recovery (FLAIR), T2, or diffusion-weighted images, patchy contrast enhancement, and increased blood flow on perfusion-weighted imaging.[45] These findings are believed to be indicative of seizure-induced cellular edema and are commonly

TABLE 6-4

### Ictal-interictal Continuum Patterns[a]

- **Any periodic discharges or spike and wave pattern that averages >1 Hz and ≤2.5 Hz for at least 10 seconds (>10 or ≤25 discharges in 10 seconds)**
- **Any periodic discharge or spike and wave pattern that averages 0.5 Hz or more and 1 Hz or less for at least 10 seconds with a plus modifier[b] or fluctuation[c]**
- **Any lateralized rhythmic delta activity greater than 1 Hz for at least 10 seconds with a plus modifier[b] or fluctuation**

**AND**

**Does not qualify for electrographic seizures or electrographic status epilepticus**

---

[a] Data from Hirsch LJ, et al, J Clin Neurophysiol.[41]

[b] Plus modifiers are additional features that render the ictal appearance of a pattern and include fast frequencies (+F) superimposed on either periodic discharges or rhythmic delta activity; embedded rhythmic frequencies (+R) superimposed on periodic discharges; and embedded sharp discharges (+S) superimposed on rhythmic delta activity.

[c] Fluctuation refers to 3 or more changes, not more than 1 minute apart, in frequency (by at least 0.5/s); 3 or more changes in morphology; or 3 or more changes in location by at least 1 standard interelectrode distance; with these changes not qualifying as evolving.

observed in cortical and limbic structures, specifically the hippocampus or deep structures like the pulvinar nucleus of the thalamus.[45] Although many of these findings are reversible, they can persist for weeks or longer, particularly in cases of prolonged seizures. Eventually, they either resolve or progress into focal atrophy and sclerosis. Differentiating between seizure-related findings and underlying causative lesions is not always straightforward, and repeat imaging may be required.

Typically, patients who present with convulsive status epilepticus awaken gradually after the motor features of seizures resolve. However, if their level of consciousness does not improve by 20 to 30 minutes after the cessation of movements, this could be due to a prolonged postictal state, sedation related to medications, or nonconvulsive status epilepticus, so electroencephalography must be performed urgently.

**KEY POINT**

- There is a need for a structured therapeutic and diagnostic approach to status epilepticus, starting with the assessments of airway, breathing, circulation, disability, and exposure (ABCDE).

### Nonconvulsive Status Epilepticus

When there is clinical suspicion of nonconvulsive status epilepticus, electroencephalography is needed to make the diagnosis. Nonconvulsive status epilepticus includes both electrographic and electroclinical status epilepticus. Electrographic seizures are largely based on the Salzburg criteria (TABLE 6-5). An electroclinical seizure is defined as any EEG pattern that has a definitive clinical correlate that is time-locked to the EEG pattern or EEG and clinical improvement with parenteral antiseizure medication. Electrographic status epilepticus and electroclinical status epilepticus are defined as electrographic seizures or electroclinical seizures, respectively, lasting 10 consecutive minutes or longer, amounting to 20% or more of any 60-minute period of recording or intermittent seizures cumulatively reaching a seizure burden of 20% or more of any 60 minutes of the recording.[40] In some cases, it is unclear whether EEG findings

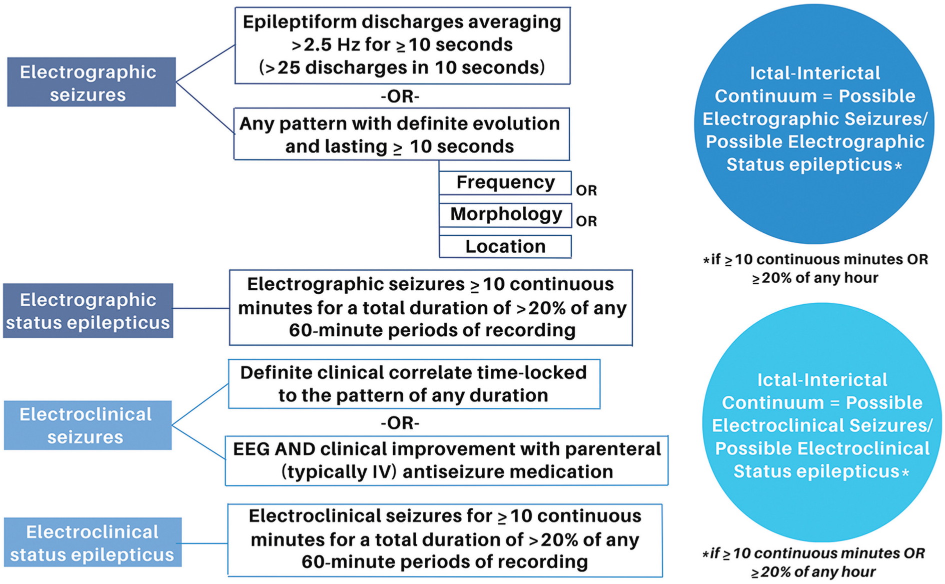

Electrographic seizures
Epileptiform discharges averaging >2.5 Hz for ≥10 seconds (>25 discharges in 10 seconds)
-OR-
Any pattern with definite evolution and lasting ≥ 10 seconds
Frequency
OR
Morphology
OR
Location
Ictal-Interictal Continuum = Possible Electrographic Seizures/ Possible Electrographic Status epilepticus*
*if ≥10 continuous minutes OR ≥20% of any hour
Electrographic status epilepticus
Electrographic seizures ≥10 continuous minutes for a total duration of >20% of any 60-minute periods of recording
Electroclinical seizures
Definite clinical correlate time-locked to the pattern of any duration
-OR-
EEG AND clinical improvement with parenteral (typically IV) antiseizure medication
Ictal-Interictal Continuum = Possible Electroclinical Seizures/ Possible Electroclinical Status epilepticus*
*if ≥10 continuous minutes OR ≥20% of any hour
Electroclinical status epilepticus
Electroclinical seizures for ≥10 continuous minutes for a total duration of >20% of any 60-minute periods of recording

FIGURE 6-5

**American Clinical Neurophysiology Society critical care EEG terminology describing electrographic and electroclinical syndromes.**

Data from Hirsch LJ, et al, J Clin Neurophysiol.[41]

are ictal. A practical approach to resolving this question is to perform an antiseizure medication trial by administering a benzodiazepine or a nonbenzodiazepine antiseizure medication loading dose and assessing the patient's EEG and clinical response. FIGURE 6-6 illustrates a suggested approach to a patient with ictal-interictal continuum).[46] A recently proposed standardized approach suggests considering among nonbenzodiazepine medications, levetiracetam, valproate, lacosamide, brivaracetam, or (where it is the only feasible antiseizure medication) fosphenytoin or phenobarbital.[47] The authors recommend administering an initial loading dose of IV nonbenzodiazepine antiseizure medication at two-thirds to three-quarters of the maximum loading dose used for status epilepticus. If the initial trial yields no response or an equivocal response after appropriate monitoring time, then the remaining one-third or one-quarter of the maximum loading dose can be administered. Additionally, the authors proposed implementing a simple clinical scale, termed the *nonconvulsive status epilepticus response scale*, for both preintervention and postintervention assessments, aiming to standardize the clinical evaluation of intubated and nonintubated patients. A trial is considered positive if both clinical and EEG improvements are seen. In some cases, clinical improvement will not be immediate and can take several hours (usually less than 24 hours). Nonconvulsive status epilepticus can be challenging to diagnose, especially if the ictal-interictal continuum is seen on EEG. When uncertain, it is recommended to conduct a trial with antiseizure medication as a diagnostic measure. If there is only EEG improvement without clinical improvement, a trial is inconclusive, which does not exclude the possibility of nonconvulsive status epilepticus but does not confirm it either. Every patient should be treated on a case-by-case basis. CASE 6-2 illustrates a patient whose EEG showed an ictal-interictal continuum and who had a positive antiseizure medication trial.

If after an antiseizure medication trial, there is still uncertainty about the ictal potential of these patterns, ancillary tests can offer guidance in the approach and management.[40] Ancillary tests that can help clarify whether EEG findings are ictal include brain imaging, such as MRI, CT perfusion, and positron emission tomography (PET) scans; neuron-specific enolase; intracortical electroencephalography; brain tissue oxygenation; and cerebral microdialysis.

TABLE 6-5

**Salzburg Criteria for Electrographic Seizures**

Epileptiform discharges averaging more than 2.5 Hz for 10 or more seconds (>25 discharges in 10 seconds)

**OR**

Any repetitive or periodic pattern with definite evolution and lasting 10 or more. *Evolution* is defined as at least two unequivocal, sequential changes in frequency, morphology, or location

- Evolution in frequency: at least two consecutive changes in the same direction by at least 0.5 Hz
- Evolution in morphology: at least two consecutive changes to a novel morphology
- Evolution in location: sequentially spreading into or sequentially spreading out of at least two different standard 10-20 electrode locations

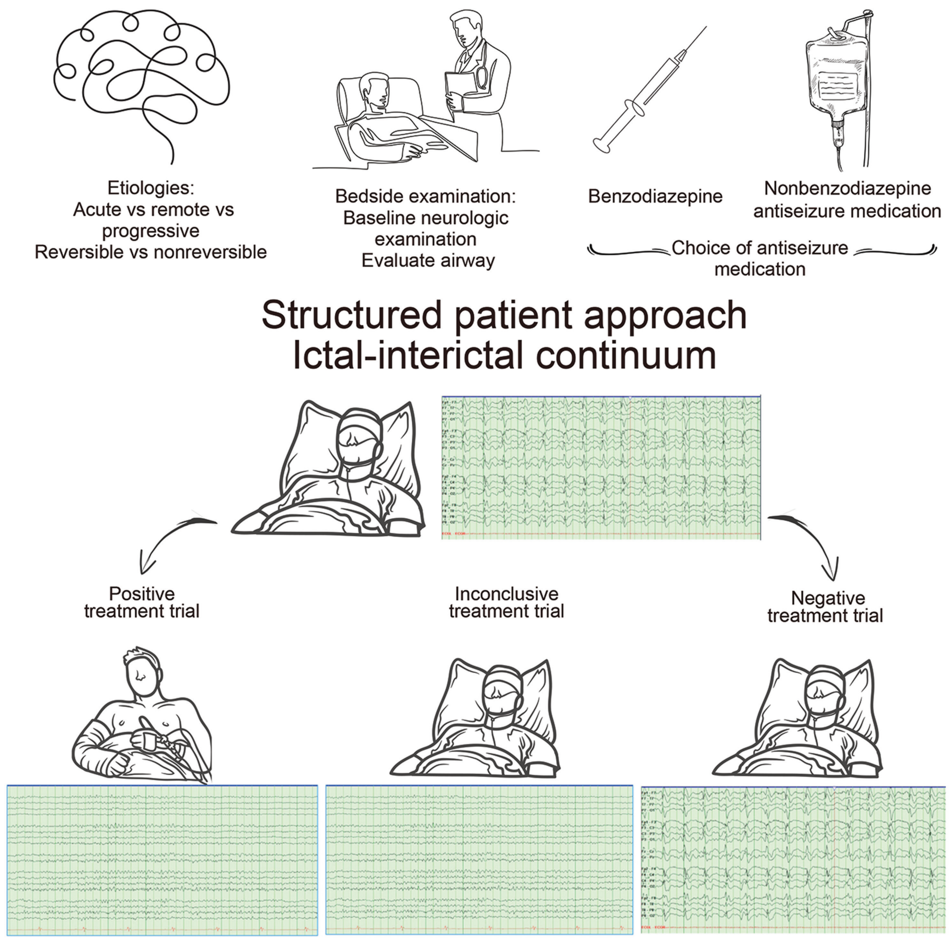

Etiologies:
Acute vs remote vs progressive
Reversible vs nonreversible
Bedside examination:
Baseline neurologic examination
Evaluate airway
Benzodiazepine
Nonbenzodiazepine antiseizure medication
Choice of antiseizure medication
Structured patient approach
Ictal-interictal continuum
Positive treatment trial
Inconclusive treatment trial
Negative treatment trial

**FIGURE 6-6**
Structured approach to the ictal-interictal continuum.

KEY POINT

- Nonconvulsive status epilepticus can be challenging to diagnose, especially if the ictal-interictal continuum is seen on the EEG. When uncertain, it is recommended to conduct a trial with benzodiazepines as a diagnostic measure.

Evidence of heightened neuronal activity or increased neuronal metabolic stress could be indicative of seizures.

CASE 6-3 describes a complex patient with ictal-interictal continuum in which ancillary testing (MRI) supported aggressive medical management.

## MANAGEMENT OF STATUS EPILEPTICUS

Status epilepticus is a neurologic emergency, and prolonged status epilepticus can increase the risks of cardiac and respiratory complications, neuronal loss, brain injury (as observed in neuroimaging studies), and mortality.[48–50]

An urgent and staged approach to treatment in which different medications are used in early (stage 1), established (stage 2), refractory (stage 3), and super-refractory status epilepticus (stage 4) has been recommended.[3]

### Stage 1 (5 to 10 Minutes)

Benzodiazepines are the cornerstone of management in the early phase of status epilepticus. There are few high-quality randomized controlled trials for the management of status epilepticus. However, among the available trials, the use of benzodiazepines as a first-line medication for status epilepticus management

## CASE 6-2

**A 64-year-old woman was admitted to the hospital because of community-acquired pneumonia and was started on ceftriaxone. The day after admission, she was found to have an altered mental status, to be poorly responsive to commands, and to have minimal verbal output. EEG was ordered because of concern for nonconvulsive seizure and showed persistent continuous 2-Hz to 2.5-Hz generalized periodic discharges with triphasic morphology consistent with ictal-interictal continuum (FIGURE 6-7A). The decision was made to do a benzodiazepine trial and lorazepam 2 mg was given. FIGURE 6-7B demonstrated improvement of the EEG seconds after lorazepam administration. Five minutes after the trial, the patient was more conversant and alert. The EEG demonstrated resolution of the generalized periodic discharges (FIGURE 6-7C). The benzodiazepine trial was deemed to be positive, and the patient was started on levetiracetam to prevent recurrence of electroclinical status epilepticus.**

---

**COMMENT**

Generalized periodic discharges at 2 Hz to 2.5 Hz for more than 10 seconds fulfill the criteria of ictal-interictal continuum. This is considered possible status epilepticus when it persists for 10 minutes or longer or for 20% or more of an hour. After the administration of 2 mg of lorazepam, there was EEG and clinical improvement, establishing the diagnosis of electroclinical status epilepticus.

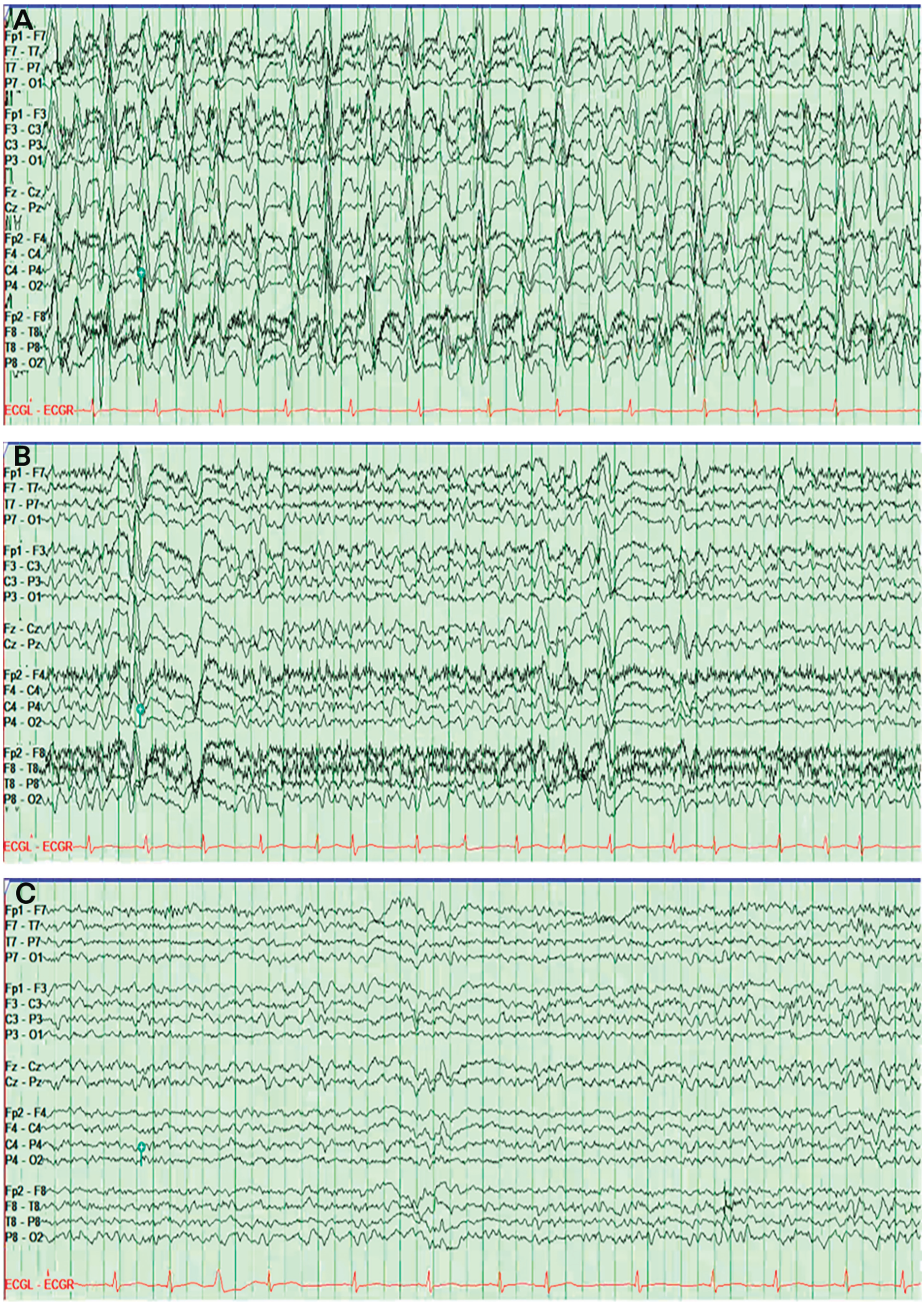

A
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECGL - ECGR
B
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECGL - ECGR
C
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECGL - ECGR

**FIGURE 6-7**

EEG findings for the patient in CASE 6-2. *A*, Ictal-interictal continuum. *B*, Improvement in generalized periodic discharges after a benzodiazepine trial. *C*, Resolution of generalized periodic discharges. These EEGs have a sensitivity of 7 μV/mm and a time base of 30 mm/s.

## CASE 6-3

A 74-year-old man with a history of hypertension was admitted to the hospital for septic shock secondary to pneumonia. He required 3 days of mechanical ventilation. After extubation, he was noted to have an altered mental status, which gradually worsened over 2 days, and then he became unresponsive and had a seizure characterized by right eye deviation, rightward head version, and right face and right leg twitching. He was reintubated because of hypoxic respiratory failure. CT of his head was unremarkable. Comprehensive workup was negative and CSF analysis showed a slight increase in protein, with normal cell count and glucose. EEG showed persistent 1-Hz to 1.5-Hz left polyphasic lateralized periodic discharges with superimposed fast activity over the left posterior quadrant (FIGURE 6-8A). MRI of the brain showed T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity within the pulvinar nucleus of the left thalamus (FIGURE 6-9A) and left posterior parafalcine gyrus (FIGURE 6-9B). These changes were associated with mild swelling and corresponding restricted diffusion on diffusion-weighted images (FIGURE 6-9C and 6-9D).

He was given 4 mg of lorazepam with minimal improvement of EEG and no improvement clinically. To achieve seizure control, he was loaded with 4.5 g of levetiracetam (60 mg/kg, maximum dose of 4.5 g) and started on midazolam at 0.2 mg/kg/h and propofol 40 µg/kg/min. Because of the persistence of the discharges despite these interventions, propofol was discontinued and ketamine was started and increased up to 4 mg/kg/h, while the midazolam dose was increased up to 1.2 mg/kg/h. Concomitantly, he was loaded with 400 mg of lacosamide and 3 g (40 mg/kg, maximum dose of 3 g) of valproate. His valproate level 3 hours after the load was 80 µg/mL, so he was given an additional smaller load of 10 mg/kg to achieve a level of 120 µg/mL. Burst suppression was achieved with a background of 3 to 5 seconds of interburst suppression and 2 to 4 seconds of bursts (1-Hz to 2-Hz lateralized periodic discharges with superimposed fast activity) (FIGURE 6-8B). Because periodic discharges persisted despite high doses of midazolam and ketamine, these drips were discontinued, and a pentobarbital infusion was started and increased to 2 mg/kg/h, which led to total suppression of the EEG background. This was continued for 48 hours. Before pentobarbital discontinuation, he was loaded with 20 mg/kg of phenobarbital and started on 130 mg 2 times a day maintenance dose, which was weaned off during hospitalization. Lateralized periodic discharges with superimposed fast activity did not recur after stopping pentobarbital (FIGURE 6-8C). He was hospitalized for two months and required a tracheostomy and percutaneous endoscopy gastrostomy tube, but he was discharged to an acute rehabilitation facility. On discharge, he was awake and following commands, but he had significant weakness in all extremities because of critical illness polyneuropathy and myopathy.

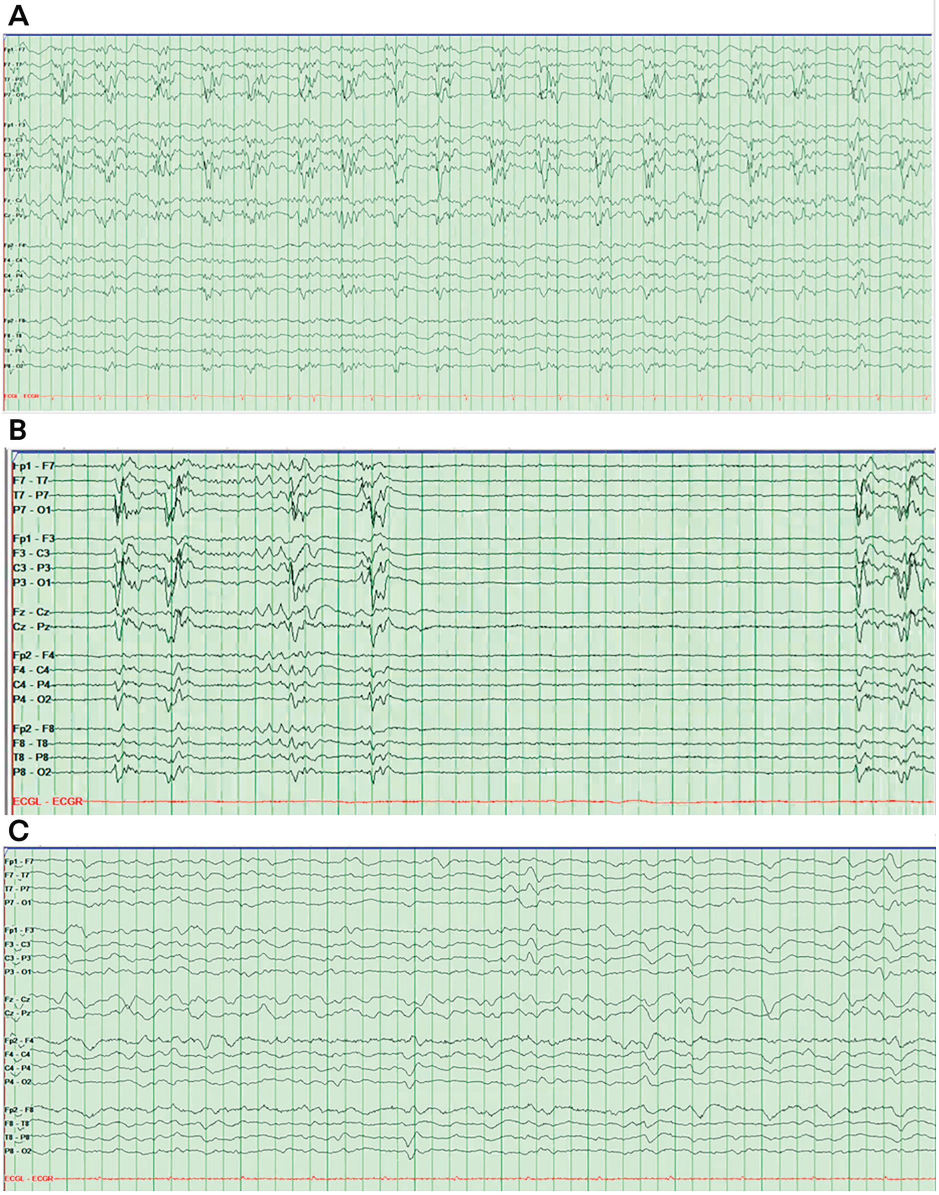

A
B
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECGL - ECGR
C

**FIGURE 6-8**
EEG findings for the patient in CASE 6-3. *A*, EEG showing 1- to 1.5-Hz left polyphasic lateralized periodic discharges with superimposed fast activity over the left posterior quadrant. *B*, EEG showing burst suppression with bursts of 1- to 2-Hz lateralized periodic discharges with superimposed fast activity. *C*, EEG showing diffuse slowing with absence of epileptiform discharges. These EEGs have a sensitivity of 7 μV/mm and a time base of 30 mm/s.

**COMMENT**

The neuroimaging findings in this case suggested seizure-induced cellular edema and the EEG findings were compatible with ictal-interictal continuum. Antiseizure medications were escalated as he progressed through the stages of status epilepticus. Immunotherapy was not considered because there was an acute etiology deemed responsible for his status epilepticus (pneumonia with septic shock).

CONTINUED ON PAGE 704

## CASE 6-3

CONTINUED FROM PAGE 703

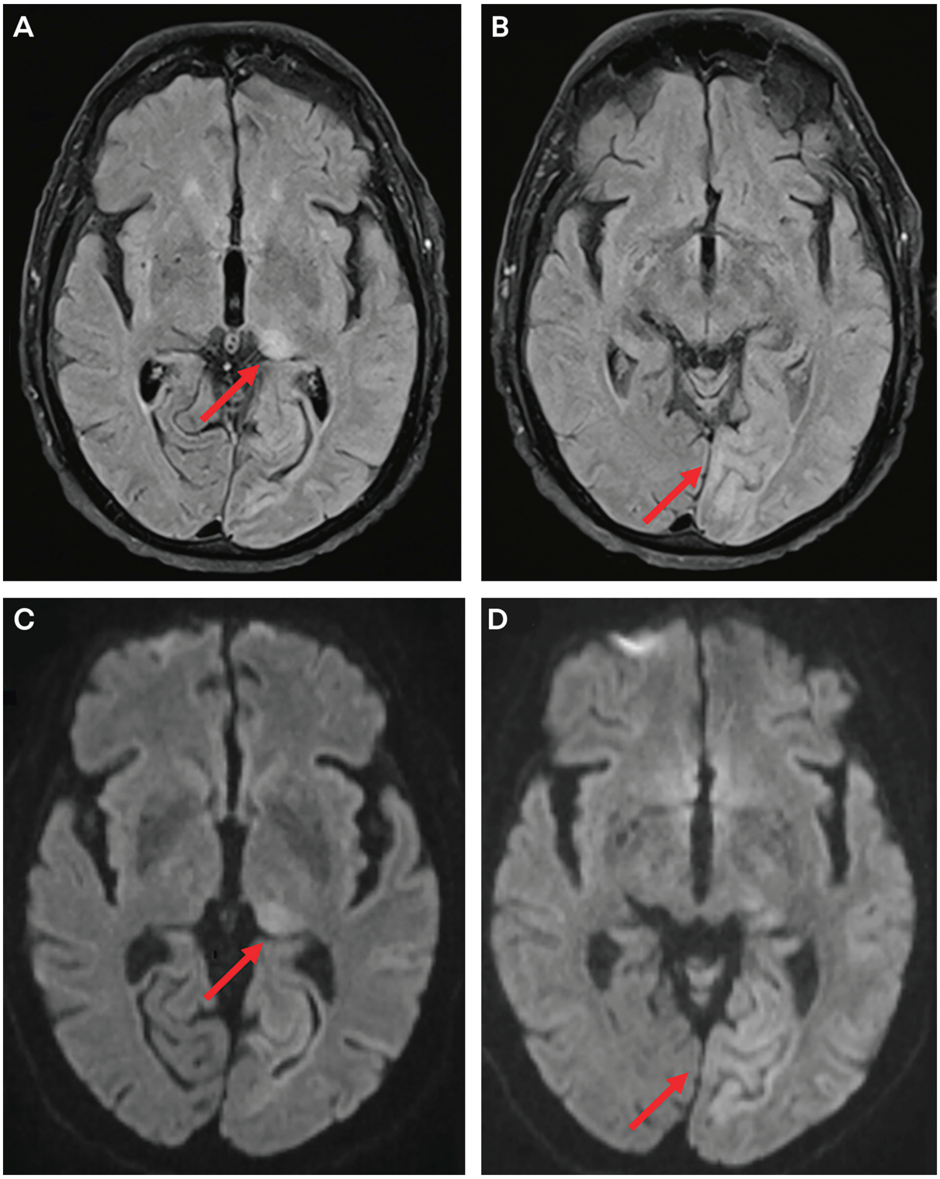


**FIGURE 6-9**
Axial MRI findings for the patient in CASE 6-3. *A*, fluid-attenuated inversion recovery (FLAIR) MRI showing hyperintensity in the pulvinar nucleus of the left thalamus (*arrow*). *B*, FLAIR MRI showing hyperintensity in the left posterior parafalcine gyrus (*arrow*). *C*, Diffusion-weighted imaging showing mild hyperintensity of the pulvinar nucleus of the left thalamus (*arrow*). *D*, Diffusion-weighted imaging showing mild hyperintensity of the left posterior parafalcine gyrus (*arrow*).

has the highest level of evidence. Three randomized controlled trials have examined the efficacy of benzodiazepines, including their use in prehospital treatment.[49,51,52] A study comparing out-of-hospital administration of 2 mg to 4 mg of IV lorazepam versus 5 mg to 10 mg of IV diazepam or placebo showed that both benzodiazepines were more successful in treating status epilepticus before emergency department arrival than placebo.[49] Additionally, the odds ratio for status epilepticus termination in the lorazepam group was 1.9 (95% CI, 0.8 to 4.4) as compared with the diazepam group. Although the confidence interval included the null hypothesis, there was a trend favoring lorazepam to diazepam.[49]

The most effective first-line treatment is an adequate dose of benzodiazepine. The primary factor contributing to the lack of success in stage 1 status epilepticus seizure cessation is benzodiazepine underdosing. A landmark study of IV lorazepam versus intramuscular midazolam in the prehospital management of status epilepticus[48] showed that intramuscular midazolam was noninferior to IV lorazepam in terminating seizures before arrival to the emergency department. Interestingly, IV lorazepam was superior to intramuscular midazolam in time from active treatment to cessation of convulsion (1.6 versus 3.3 minutes), but when analyzing from the time of opening the box containing the study drug kit to active treatment, intramuscular midazolam was superior to IV lorazepam (1.2 versus 4.8 minutes). The latter indicates that establishing IV access in patients who are having seizures can be challenging and time consuming, hence the increased time in the lorazepam group in opening the box containing the study drug kit to active treatment analysis. These findings suggest that, when IV access is available, IV lorazepam is the preferred treatment for status epilepticus. However, when IV access is not feasible, intramuscular midazolam is an effective alternative. Other routes of midazolam administration are buccal or intranasal (midazolam nasal spray). Additionally, rectal administration of diazepam should be considered when appropriate.[1] If none of the alternatives are available and there is no IV access, intramuscular lorazepam could also be administered; however, intramuscular delivery of lorazepam has slower absorption of the drug and lower maximum serum concentration than IV administration (48 ng/mL versus 70 ng/mL).[53]

A study analyzing benzodiazepine administration in patients enrolled in ESETT (Established Status Epilepticus Treatment Trial) showed that lorazepam and midazolam were adequately dosed only 24% and 14% of the time, respectively.[54] The cautious approach of withholding benzodiazepines may stem from concerns regarding the potential risk of respiratory depression following their administration. However, it is worth noting that there was a trend toward a higher incidence of respiratory depression in patients with untreated status epilepticus as opposed to those who received appropriate doses of benzodiazepines.[49] The importance of appropriate benzodiazepine dosing was evidenced in the SAMUKeppra (prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus) trial,[55] which aimed to evaluate the effectiveness of adding 2.5 g of IV levetiracetam to 1 mg of IV clonazepam in the prehospital treatment for status epilepticus. Although the study did not demonstrate significant benefits of the addition of levetiracetam, the study showed a high response rate in the clonazepam group (84%), surpassing the response rates observed in previous trials using IV lorazepam (up to 65%).[48,52] The trial protocol allowed for a second dose of 1 mg of IV

**KEY POINTS**

- **The most effective first-line treatment of status epilepticus is an adequate dose of benzodiazepine. The primary factor contributing to the lack of success in stage 1 status epilepticus seizure cessation is benzodiazepine underdosing.**

- **Phenytoin or fosphenytoin, valproate, and levetiracetam have the same efficacy and safety profile in the management of stage 2 status epilepticus.**

clonazepam to be administered before assessing seizure cessation within 15 minutes of treatment initiation. This suggests that the high success rate achieved with a higher dose of clonazepam (total dose of 2 mg of clonazepam which is approximately 4 mg of lorazepam) may have overshadowed the potential efficacy of adding levetiracetam. Thus, the study implies that early treatment initiation and the use of adequate benzodiazepine doses are the most effective therapeutic approaches. TABLE 6-6 shows the recommended dosing of benzodiazepines as first-line antiseizure medications.

### Stage 2 (10 to 30 Minutes)

Up to one-third of patients will not respond to emergent benzodiazepine therapy and will progress to established status epilepticus, requiring additional IV antiseizure medications. The second-line antiseizure medications commonly used include phenytoin or fosphenytoin, valproate, phenobarbital, levetiracetam, and lacosamide. Currently, no evidence suggests the superiority of any of these drugs over the others. Phenytoin or fosphenytoin, valproate, and levetiracetam have the same efficacy and safety profile in the management of stage 2 status epilepticus. The ConSEPT (levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children) and EcLiPSE (levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus) trials were two randomized clinical trials conducted in pediatric populations to compare the efficacy of phenytoin (20 mg/kg) with levetiracetam (40 mg/kg) in treating convulsive status epilepticus. These studies did not show that levetiracetam was superior to phenytoin.[56,57] It is worth noting that both trials used a lower loading dose of levetiracetam, which was below the recommended dose of 60 mg/kg suggested by the American Epilepsy Society.[58]

TABLE 6-6 **Suggested Treatment for Status Epilepticus Stage 1**

| Medication | Route of administration and dose | Elimination half-life |
|---|---|---|
| **Diazepam** | IV: 0.15-0.2 mg/kg/dose; may repeat once<br>Rectal: 0.2-0.5 mg/kg; maximum of 15-20 mg per dose, single dose<br>Intranasal: 0.2 mg/kg, may be repeated in 4 hours; 28-50 kg (10 mg via one 10-mg device), 51-75 kg (15 mg via two 7.5-mg devices), 76 kg or greater (20 mg via two 10-mg devices) | 48 hours (rapidly redistributes out of the brain, so short duration in status) |
| **Lorazepam** | IV (preferred): 0.1 mg/kg, can repeat once, maximum dose is 4 mg<br>Can be given IM in the absence of IV access, but this can be painful and absorption is reduced to 70% | 12-24 hours |
| **Midazolam** | IV or IM (IM has good absorption): 0.2 mg/kg, maximum dose of 10 mg<br>Intranasal: one 5-mg dose, may repeat in 10 minutes in opposite nostril<br>Buccal: 0.5 mg/kg[a] | 90-150 minutes |

---

[a] Not approved by the US Food and Drug Administration (FDA).

More recently, the ESETT trial randomized patients older than 2 years to one of three treatments: (1) fosphenytoin 20 phenytoin equivalents/kg, valproate 40 mg/kg, and levetiracetam 60 mg/kg. The ESETT trial aimed to generate scientific evidence to determine the selection of second-line antiseizure medications based on their efficacy and safety profiles. The primary outcome was cessation of clinically evident seizure activity and improvement of level of consciousness at 60 minutes from second-line antiseizure medication administration. The trial ended early because it met the predefined criterion for futility of finding one drug to be superior or inferior. Seizures were controlled in

**Suggested Treatment for Status Epilepticus Stage 2** **TABLE 6-7**

| Medication | Loading dose | Maintenance dose | Note |
|---|---|---|---|
| **Fosphenytoin** | 20 mg phenytoin equivalents (PE)/kg IV (maximum of 1500 mg); maximum rate of 150 mg/min<br>Second dose: 5-10 mg PE/kg[a] IV | 5-7 mg PE/kg/d intravenously or orally in 2-4 divided doses | Side effects: hypotension, perineal pruritus<br>Blood levels: total fosphenytoin, up to 20 μg/mL; free fosphenytoin, 2 μg/mL |
| **Lacosamide** | 8 mg/kg (maximum of 600 mg) IV | 200-300 mg every 12 hours | Dose adjustment in severe renal or hepatic impairment (maximum 300 mg/d)<br>Side effects: may prolong PR interval (do not use if PR is longer than 200 ms), hypotension |
| **Levetiracetam** | 60 mg/kg IV (maximum of 4500 mg) | 1000-6000 mg/d in 2-3 doses | Adjust dose for renal function<br>Side effects: sedation, agitation, aggression |
| **Phenobarbital** | 20 mg/kg IV (maximum rate of 60 mg/min)<br>Second dose: 5-10 mg/kg (maximum rate of 60 mg/min)[a] | 1-3 mg/kg/d in 2-3 divided doses | Side effects: hypotension, respiratory depression, metabolic acidosis<br>Blood level target: 15-40 μg/mL |
| **Phenytoin** | 20 mg/kg IV (maximum rate 50 mg/min)<br>Second dose: 5-10 mg/kg[a] | 5-7 mg/kg/d IV or orally in 2-4 divided doses | Side effects: pain, phlebitis, purple glove syndrome, hypotension, bradycardia, ventricular arrhythmias, cardiac nodal depression, metabolic acidosis<br>Blood levels in the presence of normal albumin levels: total phenytoin, 15-20 μg/mL; free phenytoin, 1.5-2 μg/mL |
| **Sodium valproate** | 40 mg/kg IV over 10 min (maximum of 3000 mg); maximum rate of 60 mg/kg/min<br>Second dose: 20 mg/Kg IV[a] | Start 10-15 mg/kg/d in 3-4 divided doses | Beware of concurrent carbapenem use because it drastically lowers blood levels; avoid concomitant administration with phenytoin and phenobarbital because of drug interactions<br>Side effects: tremor, hyperammonemia, thrombocytopenia, hepatic toxicity, pancreatitis<br>Blood level goal: 50-140 μg/mL |

---

[a] Second dose if seizures persist.

about 50% of patients who received any of these antiseizure medications and rates of adverse events were similar across the treatment arms.

A network meta-analysis of five randomized controlled trials that included 349 participants with established status epilepticus compared treatment with sodium valproate (20 mg/kg to 30 mg/kg), phenytoin (20 mg/kg), diazepam (0.2 mg/kg, then 4 mg/h), phenobarbital (20 mg/kg, then 100 mg every 6 hours), lacosamide (400 mg), and levetiracetam (20 mg/kg).[59] This study found that phenobarbital was superior to the other antiseizure medications for established status epilepticus cessation, but it had the worst performance with respect to safety endpoints (hypotension and respiratory depression). However, lacosamide and valproate performed better regarding safety endpoints. Given the limited number of included studies, their small sample sizes, and heterogeneity in the etiology of status epilepticus, caution should be exercised when interpreting the findings of this meta-analysis. It is important to consider the variations in dosages when interpreting the results; the phenobarbital dosage used in the study included in the meta-analysis was 20 mg/kg, followed by 100 mg every 6 hours, which is higher than the maximal dose (15 mg/kg as a single dose) recommended by the American Epilepsy Society guidelines.[58] Additionally, sodium valproate and levetiracetam dosages were lower (20 mg/kg to 30 mg/kg and 20 mg/kg, respectively) than the recommended guidelines (40 mg/kg and 60 mg/kg, respectively.)[58] Because of the limited evidence supporting the use of specific second-line treatments for established status epilepticus, there is currently no consensus on a single recommended drug.

TABLE 6-8 Additional Antiseizure Medication for Any Stage of Status Epilepticus

| Medication | Loading dose | Maintenance dose | Note |
|---|---|---|---|
| **Brivaracetam** | 100-200 mg, oral or IV | 100 mg every 12 hours | IV administration only for 3 days after status epilepticus, then change to oral administration; higher doses have been used, but are not recommended<br>Side effects: sedation |
| **Clobazam** | 60 mg oral | 20 mg/d 2 times a day (10-60 mg/d) | Oral or enteral administration only; load only in patients with protected oral airway<br>Side effects: sedation, respiratory depression |
| **Perampanel** | Variable, up to 32 mg oral | 2-12 mg/d in divided doses | Major substrate for CYP3A4, so higher doses may be required with inducers such as carbamazepine, phenytoin, or oxcarbazepine |
| **Pregabalin** | 450-600 mg oral | 75-100 mg/d | Studied for cyclic seizures<br>Side effects: sedation, respiratory depression |
| **Topiramate** | 200-400 mg oral | 300-1600 mg/d every 12 hours | Oral or enteral administration only<br>Side effects: metabolic acidosis, nephrolithiasis |
| **Zonisamide** | Three times the maintenance dose, administered in two divided doses, 6 hours apart | 100-300 mg/d | Side effects: metabolic acidosis, nephrolithiasis, gastrointestinal disorders |

Each available drug has its unique advantages and disadvantages that vary depending on the clinical situation. The selection of a second-line drug primarily depends on factors such as its accessibility, patient comorbidities, and the specific clinical context. Refer to TABLE 6-7 for recommended dosing of second-line antiseizure medications.

### Stage 3 (30 to 60 Minutes) and Stage 4 (Longer Than 24 Hours)

Status epilepticus is considered refractory when the first- and second-line treatments fail and seizures continue or recur. In this stage, the primary approach to treatment involves the continuous IV administration of anesthetic drugs. However, there is a lack of clear evidence to guide the treatment of refractory status epilepticus. Additionally, observational studies have linked the continuous use of IV anesthetic drugs to independent risks, including undesirable events and even death. Therefore, the treatment choice must be carefully weighed, considering the estimated benefits and risks for each patient. In some cases of refractory status epilepticus, administering a loading dose of another antiseizure medication agent can be advantageous. Refer to TABLE 6-8 for recommended dosing of additional antiseizure medications.

**INTRAVENOUS ANESTHETICS USED TO TREAT STATUS EPILEPTICUS.** Continuous IV anesthetics that are typically used to treat refractory status epilepticus include midazolam, propofol, pentobarbital (thiopental is often used in Europe), and ketamine (TABLE 6-9). The initial continuous IV anesthetic is typically

**Continuous IV Anesthetics for Status Epilepticus Stage 3 and Stage 4** TABLE 6-9

| Medication | Loading dose | Maintenance dose | Side effects |
|---|---|---|---|
| **Ketamine** | 1.5 mg/kg every 5-10 minutes until seizure cessation; maximum of 4.5 mg/kg | Start 1 mg/kg/h, then bolus and increase rate by 0.5-1 mg/kg/h until seizure cessation; maximum of 10 mg/kg/h | Nausea, emesis, dissociation, hypertension, metabolic acidosis in combination with certain medications is administered; avoid in patients with cardiac disease |
| **Midazolam** | 0.2 mg/kg IV over 2-5 minutes; rebolus 0.2 mg/kg every 5-10 min until seizure cessation; maximum load of 2 mg/kg | Start 0.1 mg/kg/h then bolus 0.1 mg/kg and increase the rate by 0.05-0.1 mg/kg/h; maximum dose of 2.9 mg/kg/h | Hypotension; active metabolite renally eliminated, prolonged duration in renal impairment |
| **Pentobarbital** | 10 mg/kg IV; rebolus 5 mg/kg until seizure cessation; maximum of 50 mg/min | Start 1 mg/kg/h, bolus and increase rate by 0.5-1 mg/kg/h; maximum of 4 mg/kg/h | Hypotension, ileus, myocardial suppression, immunosuppression, thrombocytopenia, metabolic acidosis, hyperkalemia |
| **Propofol** | 1-2 mg/kg IV over 3-5 minutes; rebolus every 5-10 minutes until seizure cessation; maximum load of 10 mg/kg | 20-200 μg/kg/min | Hypotension, hypertriglyceridemia, pancreatitis; monitor for propofol infusion syndrome (metabolic acidosis, rhabdomyolysis, cardiac arrest); use caution when using high doses (>80 μg/kg/min) for long durations (>48 hours); avoid in patients allergic to soy and egg; nutrition consult recommended because of high calorie intake |

midazolam or propofol, both GABA agonists.[60] There are no prospective studies comparing propofol versus midazolam. A 2022 multicenter retrospective study showed that midazolam and propofol have comparable efficacy and safety profiles.[61] Hence, the decision to use midazolam versus propofol should be made based on the medication profile, side effects, and dose needed to achieve seizure cessation. Propofol side effects include hypertriglyceridemia, hypotension, and propofol infusion syndrome. Propofol infusion syndrome is a life-threatening emergency characterized by cardiac arrhythmias, rhabdomyolysis, metabolic acidosis, and cardiovascular collapse. Propofol infusion syndrome is a rare complication of propofol and is generally seen with prolonged high-dose infusion rates. Midazolam side effects include prolonged sedation, tachyphylaxis, and hypotension. One approach is to initiate treatment with both propofol and midazolam to obtain a synergistic GABA agonism effect, along with potentially benefiting from the NMDA antagonism that propofol offers.[62] This approach allows for the possibility of discontinuing propofol later if higher doses are required to effectively manage refractory status epilepticus while continuing to increase the dosage of midazolam and add ketamine.

There is no preferred anesthetic agent when treating refractory status epilepticus (stage 3 and stage 4). Midazolam and propofol could be started on initially, and when patients become refractory to these options, consider adding ketamine. Ketamine, an NMDA antagonist, has emerged as a viable alternative to conventional IV anesthetic agents, but limited knowledge exists regarding its independent benefits due to its frequent addition to other continuous infusions. A recent retrospective study of 68 patients with super-refractory status epilepticus found that 55 patients (81%) experienced a reduction in seizure burden by at least 50% within 24 hours of initiating ketamine treatment.[63] Furthermore, complete cessation of seizures was observed in 43 patients (63%). The use of ketamine was found to be associated with stable mean arterial pressure and a decrease in the need for vasopressor medications over time. Indeed, one notable advantage of ketamine, in comparison to other anesthetics, is its absence of cardiovascular depression. In fact, ketamine's sympathomimetic effects can lead to hypertension and tachycardia, so it should be used with caution in patients with a history of severe cardiovascular disease. Ketamine may also induce hypersalivation, which should not be mistaken for increased respiratory secretions. Although concerns regarding increased intracranial pressure with ketamine have been theorized, the study did not identify any effect of ketamine on intracranial pressure, cerebral blood flow, or cerebral perfusion pressure in 11 patients with cerebral physiologic data monitoring.[63]

Similar results to the positive response to ketamine have been previously published in the adult and pediatric populations. Zeiler and colleagues[64] performed a systematic review that showed up to 56.5% of adults and 63.5% of pediatric patients with refractory status epilepticus had seizure control after starting ketamine. There is growing interest in using ketamine not only early during stage 3 of status epilepticus but also as a second-line treatment option because of its pharmacologic targets, relevance to the pathophysiology of status epilepticus, and the observed upregulation of NMDA receptors, which begins within minutes after the onset of status epilepticus.[65] In 2019, a pediatric hospital in Italy incorporated ketamine as a second-line antiseizure medication into their algorithm for managing status epilepticus (FIGURE 6-10). The decision to include ketamine in the protocol was based on a comprehensive literature review that

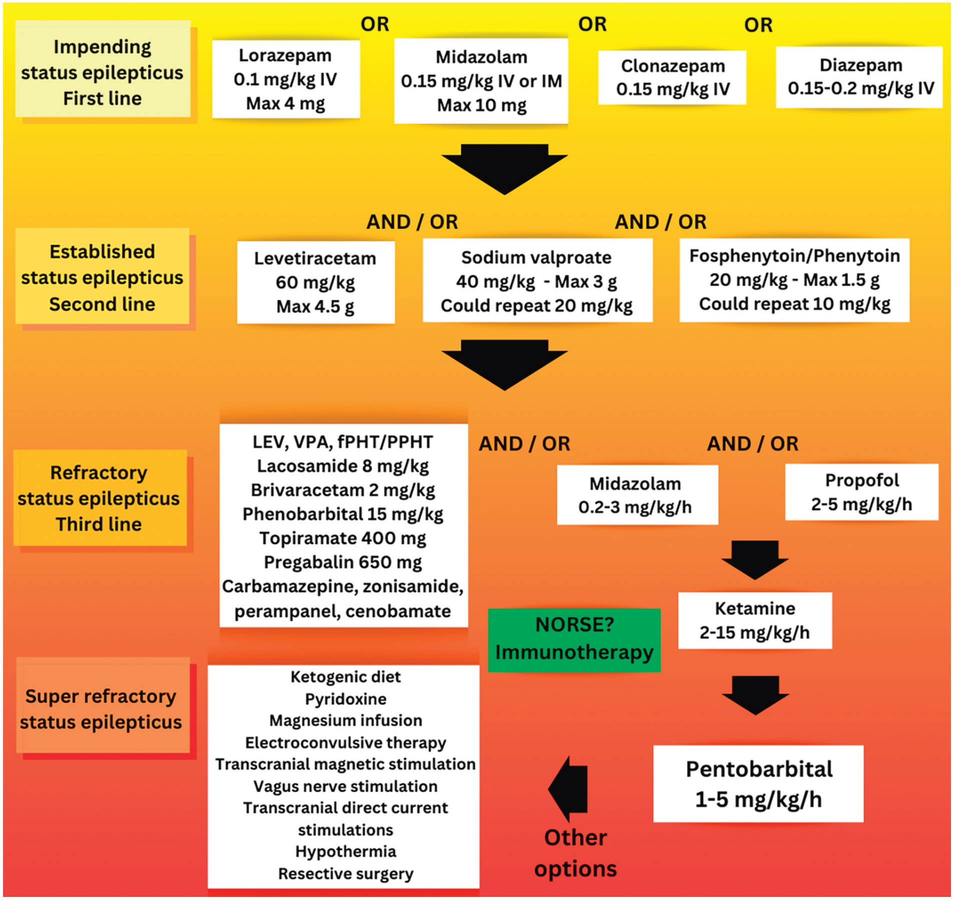

Impending status epilepticus First line
Lorazepam 0.1 mg/kg IV Max 4 mg
OR
Midazolam 0.15 mg/kg IV or IM Max 10 mg
OR
Clonazepam 0.15 mg/kg IV
OR
Diazepam 0.15-0.2 mg/kg IV
Established status epilepticus Second line
Levetiracetam 60 mg/kg Max 4.5 g
AND / OR
Sodium valproate 40 mg/kg - Max 3 g Could repeat 20 mg/kg
AND / OR
Fosphenytoin/Phenytoin 20 mg/kg - Max 1.5 g Could repeat 10 mg/kg
Refractory status epilepticus Third line
LEV, VPA, fPHT/PPHT
Lacosamide 8 mg/kg
Brivaracetam 2 mg/kg
Phenobarbital 15 mg/kg
Topiramate 400 mg
Pregabalin 650 mg
Carbamazepine, zonisamide, perampanel, cenobamate
AND / OR
Midazolam 0.2-3 mg/kg/h
AND / OR
Propofol 2-5 mg/kg/h
Ketamine 2-15 mg/kg/h
NORSE? Immunotherapy
Super refractory status epilepticus
Ketogenic diet
Pyridoxine
Magnesium infusion
Electroconvulsive therapy
Transcranial magnetic stimulation
Vagus nerve stimulation
Transcranial direct current stimulations
Hypothermia
Resective surgery
Other options
Pentobarbital 1-5 mg/kg/h

FIGURE 6-10

**Status epilepticus treatment algorithm.**

fPht = fosphenytoin; LEV = levetiracetam; Max = maximum; NORSE = new-onset refractory status epilepticus; Pht = phenytoin; VPA = valproate.

provided substantial evidence supporting its use in this context.[65] CASE 6-4 and FIGURE 6-11 illustrate a structured approach and management of a patient with refractory status epilepticus.

Pentobarbital, a GABA agonist, has fallen out of favor as a first-line anesthetic because of its side effect profile, so it is reserved for patients who fail midazolam or propofol. Safety concerns include hypotension, cardiotoxicity, paralytic ileus, hypokalemia, immune suppression, and propylene glycol toxicity. When initiating pentobarbital therapy, it is important to monitor blood pressure closely because it is very likely that vasoactive infusions will be needed. A meta-analysis examining the effectiveness of midazolam, propofol, and pentobarbital and thiopental in controlling refractory status epilepticus revealed that appropriate high doses of any anesthetic drug generally achieve control.[60] However, failure to achieve control is often attributed to either an insufficient target dose or limitations in dosing because of potential side effects. The same meta-analysis showed that midazolam had a higher rate of breakthrough seizures (3%) compared with propofol or barbiturates (1.3% and 0%, respectively), whereas barbiturates had a higher incidence of withdrawal seizures (9%) compared with propofol or midazolam (6% and 0.3%, respectively).[60] To reduce the occurrence

**KEY POINT**

- **There is no preferred anesthetic agent when treating refractory status epilepticus (stage 3 and stage 4). Midazolam and propofol could be simultaneously started initially, and if patients progress to being refractory to these options, adding ketamine should be considered.**

## CASE 6-4

**A 78-year-old man with a history of dementia and psychosis was found in bed with right-sided face and leg twitching. Emergency medical services was called and upon arrival, he was given 10 mg of intramuscular midazolam, and an additional 2 mg of lorazepam was given once IV access was established, leading to resolution of the seizure. In the emergency department, he started having seizures again, and he was given 40 mg/kg of sodium valproate and was started on a maintenance dose, with improvement in clinical seizures. Laboratory studies were significant for hyponatremia (122 mmol/L) and urinary tract infection. CT of his brain did not show any acute intracranial pathology. MRI of his brain was notable for diffuse fluid-attenuated inversion recovery (FLAIR) hyperintensities involving bilateral cerebral hemispheric white matter and diffuse parenchymal volume loss with ventriculomegaly, which was stable compared with prior imaging.**

**In the neurologic intensive care unit, EEG showed cyclic left frontal seizures. FIGURE 6-11A showed the EEG epoch before seizure onset, and FIGURE 6-11B showed the epoch during the seizure. The quantitative EEG, seen as a 1-hour period on the left side of FIGURE 6-11A and 6-11B, and a 6-hour period in FIGURE 6-11C, showed he was having three to four seizures per hour lasting 4 to 5 minutes each with no clinical correlation, which is compatible with electrographic status epilepticus (seizure total duration of 20% or more of any 60 minutes; each upslope and downslope in each trend is a seizure). He was given a load of lacosamide 400 mg and started on maintenance lacosamide. He required intubation because of impending hypoxia given the increased frequency of seizures, and he was started on midazolam, which was increased up to 0.2 mg/kg/h, and propofol infusions up to 20 μg/kg/min, which led to cessation of status epilepticus.**

---

### COMMENT

This case illustrates the structured approach and management of a patient with refractory status epilepticus. The patient's status epilepticus four axes were the following:

1. Semiology: right face and leg twitching with decreased sensorium, compatible with focal motor seizures with impaired awareness
2. Etiology: dementia with superimposed acute triggering etiologies (hyponatremia and urinary tract infection)
3. EEG correlates: left frontal beta range discharges
4. Age: older age (60 years or older)

The patient received appropriate doses of benzodiazepine as the initial treatment, followed by the administration of adequate loads of second-line agents (levetiracetam and lacosamide), and adequate anesthetic agents were used for the management of refractory status epilepticus.

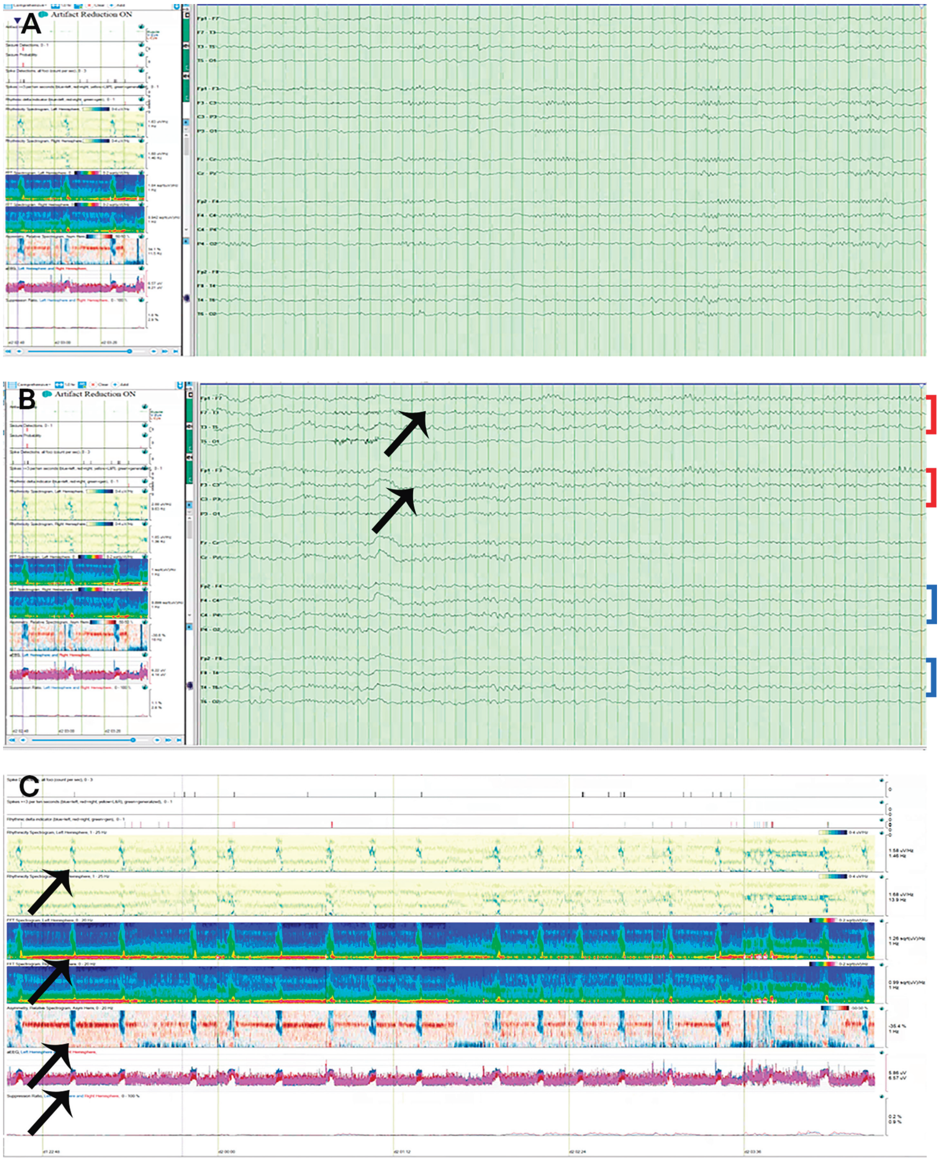

A
Artifact Reduction ON
B
Artifact Reduction ON
C

**FIGURE 6-11**

EEG findings for the patient in **CASE 6-4**. *A*, The EEG shows no evidence of epileptiform discharges before seizure onset. *B*, The EEG shows seizure onset (*arrows*); notice the acute onset of beta frequency discharges over the left frontal polar region: Fp1, F7, F3 (*red brackets* versus *blue brackets*). *C*, A quantitative EEG over a 6-hour period shows status epilepticus (*arrows*).

of withdrawal seizures, a safe transition from pentobarbital to phenobarbital can be implemented during the weaning process.[66]

**DEPTH AND DURATION OF EEG SUPPRESSION IN SUPER-REFRACTORY STATUS EPILEPTICUS.** In general, studies have found that early initiation and rapid upward titration of continuous IV anesthetics lead to more successful status epilepticus control and are associated with good outcome, even at high doses of midazolam.[67,68] The intensity and duration of the continuous infusion of IV anesthetic drugs should be guided by continuous EEG monitoring. The extent of suppression needed is not entirely clear, but typically, the goal is to maintain

**TABLE 6-10** Alternative Treatments for Super-refractory Status Epilepticus[a]

**Immunomodulatory agents (eg, adrenocorticotropic hormone, IV immunoglobulin, plasma exchange, steroids)**

- Consider early in the treatment of new-onset refractory status epilepticus (NORSE), especially if autoimmune encephalitis is suspected
- The STATUS (SAGE-547 Treatment as Adjunctive Therapy Utilized in Status Epilepticus) trial[74] studied the use of allopregnanolone, a positive allosteric modulator of γ-aminobutyric acid (GABA) receptors, in status epilepticus and found no significant difference in efficacy for seizure cessation between the control and intervention groups
- The Randomized Therapy in Status Epilepticus (RAISE) trial[70,75] is an ongoing study evaluating IV ganaxolone, an allopregnanolone analogue that modulates both synaptic and extrasynaptic $GABA_A$ receptors, in patients with refractory status epilepticus

**Ketogenic diet**

- An anticonvulsant effect may be attributed to increased synthesis of glutamine and GABA
- A multidisciplinary approach should be instituted when using the ketogenic diet because the introduction of hidden carbohydrates can cease ketosis

**Magnesium infusion**

- Unclear mechanism, but thought to inhibit *N*-methyl-D-aspartate (NMDA) receptors
- Suggested regimen: initial bolus of 4 g followed by continuous infusion at 2-6 g/h, targeting serum level of 3.5 mmol/L
- Limited evidence

**Neuromodulation techniques**

- Electroconvulsive therapy
  - Commonly applied in patients with certain psychiatric diseases
  - Unclear mechanism of action in super-refractory status epilepticus, but may stimulate activation of endogenous γ-aminobutyric acid-mediated (GABA-ergic) pathways
- Transcranial magnetic stimulation[71]
  - Pulsed electrical current is induced by electromagnetic induction to suppress cortical activity at low frequencies (≤1 Hz) and cortical excitability at high frequencies (≥5 Hz)
  - Possible cortical excitably modification when applied repetitively
  - There is no consensus on what protocol is most effective

CONTINUED ON PAGE 715

electrographic seizure cessation for a minimum of 24 hours to 48 hours[1]; however, recent data suggest that deeper, but shorter, duration of therapeutic coma might be more beneficial.[69]

### Other Interventions to Treat Super-refractory Status Epilepticus

Several other approaches have been proposed to treat refractory status epilepticus and super-refractory status epilepticus, including immunotherapy, neuroactive steroids, neuromodulation, magnesium infusion, pyridoxine infusion, hypothermia, ketogenic diet, electroconvulsive therapy, inhaled

CONTINUED FROM PAGE 714

- **Vagus nerve stimulation**
  - Not widely used
  - A systematic review[72] found that 74% of 38 patients with refractory status epilepticus or super-refractory status epilepticus had seizure cessation after acute VNS implantation
- **Deep brain stimulation**
- **Limited evidence**
- **Some data suggest that deep brain stimulation can control seizures in patients with epilepsy**
- **Target the anterior thalamic nucleus in super-refractory status epilepticus**

**Pyridoxine (vitamin $B_6$) infusion**

- **Pyridoxine is required for the production of GABA**
- **Up to 80% of patients with established status epilepticus have pyridoxine deficiency[44]**
- **There are no clear dosing data**
- **Might be most beneficial in early status epilepticus (stage 1)**

**Resective neurosurgery[76]**

- **Consider when an epileptogenic zone has been identified**
- **Can include focal, lobar, or multilobar resection; corpus callosotomy; hemispherectomy; or multiple subpial transections, either alone or in combination with focal resection**

**Therapeutic hypothermia**

- **HYBERNATUS multicenter randomized controlled trial[77] failed to show any benefit in functional outcome at 3 months**
- **Antiseizure medication levels should be followed as hypothermia reduces drug clearance**

**Transcranial direct current stimulation**

- **Emerging data for use in super-refractory status epilepticus**
- **Recent pilot study[73] showed that 10 patients with refractory status epilepticus benefited from 2-mA, 20-minute transcranial direct current stimulation sessions (ie, a reduction of 50% of median ictal epileptiform discharge rate per patient per session and a reduction of 25% in the immediate period after the intervention)**

---

[a] Data from Ferlisi M, Shorvon S, Brain.[60]

anesthetics, transcranial direct current stimulation, and surgical intervention if a definitive seizure focus has been clearly recognized (**TABLE 6-10**).[60,70–77]

## OUTCOMES

In adults, up to one-third of patients with status epilepticus will die, one-third will have persistent neurologic deficits, and one-third will recover to baseline.[60] Persistent neurologic deficits will vary in severity: 44% will have a severe deficit, 44% will have a mild deficit, and 12% will have an undefined neurologic deficit.[60] The mortality rate has been relatively constant over the past 3 decades.[14,18,35,58,60] A European study conducted in 2016 collected data prospectively from April 2006 to July 2015 and used a combination of older and newer definitions of status epilepticus.[35] The study defined it as the occurrence of continuous or repetitive seizures, between which there is incomplete recovery of baseline clinical conditions for at least 30 minutes (using data through 2008) or 5 minutes (using data since 2008). The study revealed an overall hospital discharge mortality rate of 15.5%, with higher rates observed in refractory status epilepticus at 24.5% and super-refractory status epilepticus at 37.9%.[35] Status epilepticus morbidity and mortality increase as seizures become more refractory to medical therapy.

Another European study published in 2018[14] adopted the 2015 definition of status epilepticus, which diagnosed it when seizure activity exceeded 5 minutes for convulsive status epilepticus or 10 minutes for absence status or focal status with or without impaired consciousness.[2] This study reported a similar overall in-hospital mortality rate of 16.3% (95% CI, 12% to 21.8%) and case fatality of 39.5% for refractory status epilepticus and 37.5% for super-refractory status epilepticus. Additionally, the study demonstrated a disparity in mortality rates between sexes, with 21.8% (95% CI, 15.4% to 29.9%) mortality among women and 9.3% (95% CI, 4.8% to 16.9%) mortality among men.[14] This study's findings were consistent with previously reported in-hospital mortality rates from Europe, but higher than those reported in the United States.

A systematic review conducted in the United States in 2020[10] revealed that while the mortality rate within 30 days after status epilepticus was 21%, the in-hospital mortality rate was only 2.7%. This variation could potentially be explained by differences in end-of-life care and the use of life-sustaining measures, which may vary between the two continents. Factors associated with morbidity and mortality after status epilepticus include advanced age (60 years and older), female sex, and etiology of status epilepticus, specifically acute hypoxic brain injury, meningitis or encephalitis, and stroke.[78] Furthermore, a higher comorbidity index was found to be significantly associated with increased mortality (odds ratio, 6.79; 95% CI, 4.27 to 10.8). Comorbidities, including hypertension, diabetes mellitus, sepsis, renal failure, liver failure, extracranial malignancies, sodium imbalance, and valvular disease, were specifically identified as contributing factors.[78] Mortality is proportional to the refractoriness of status epilepticus, with a significantly higher in-hospital mortality of approximately 25% for refractory status epilepticus and approximately 39% for super-refractory status epilepticus.[35,60] Advanced age (60 years and older), female sex, and underlying cause of status epilepticus have been associated with worse outcomes at discharge.

The impact of sex on medical treatment and outcomes has been understudied. Differences in sex can affect disease presentation, symptom severity, drug metabolism, and response to treatment. A 2023 study examined sex disparities in a retrospective analysis of 762 cases of status epilepticus from two Swiss tertiary care centers revealed that women were more prone to focal nonconvulsive status epilepticus without coma, whereas men were more likely to experience status epilepticus with motor symptoms.[79] Moreover, the study investigated factors related to outcomes and found that women were less likely to be discharged home and more likely to be discharged to nursing homes or hospices. Additionally, there was a difference in sex-specific status epilepticus treatment with women being less likely than men to receive anesthetics and undergo intubation. Finally, to mitigate the impact of age differences, the authors conducted age-based propensity score matching and demonstrated that female sex was associated with a lower likelihood of returning to premorbid neurologic status. Although this study did not find an association between patient sex and mortality, it demonstrated that there are sex-related treatment differences that might affect posthospital disposition and neurorecovery.

## KEY POINTS

- **Status epilepticus morbidity and mortality increase as seizures become more refractory to medical therapy.**

- **Advanced age (60 years and older), female sex, and underlying cause of status epilepticus have been associated with worse outcomes at discharge.**

## CONCLUSION

Status epilepticus is a neurologic emergency. Timely and aggressive administration of adequate doses of benzodiazepines and antiseizure medications is crucial to aborting seizures and avoiding morbidity and mortality. There is a need for further research on new antiseizure medications and nonpharmacologic therapies to treat status epilepticus.

## REFERENCES

1 Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(1):3-23. doi:10.1007/s12028-012-9695-z

2 Trinka E, Cock H, Hesdorfer D. A definition and classification of status epilepticus-Report of the ILAE Task Force on classification of status epilepticus. Epilepsia 2015;56:1515-1523. doi:10.1111/epi.13121

3 Trinka E, Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 2017;44:65-73. doi:10.1016/j.seizure.2016.11.001

4 Chen JWY, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006;5(3):246-256. doi:10.1016/S1474-4422(06)70374-X

5 Kapur J, Elm J, Chamberlain JM. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019;381(22):2103-2113. doi:10.1056/NEJMoa1905795

6 Bleck TP. Refractory status epilepticus. Curr Opin Crit Care 2005;11(2):117-120. doi:10.1097/01.ccx.0000157079.72999.87

7 Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134(Pt 10):2802-2818. doi:10.1093/brain/awr215

8 Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018;59(4):739-744. doi:10.1111/epi.14016

9 Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol 2015;14(6):615-624. doi:10.1016/S1474-4422(15)00042-3

10 Lu M, Faure M, Bergamasco A, et al. Epidemiology of status epilepticus in the United States: a systematic review. Epilepsy Behav 2020;112:107459. doi:10.1016/j.yebeh.2020.107459

11 Romano L, Spadaro E, Sousa L, et al. Incidence of status epilepticus in adult in Argentina: A prospective, epidemiological study based in captive population. Neurologia Argentina 2011;3:18-25. doi:10.1016/S1853-0028(11)70005-2

12 Sadarangani M, Seaton C, Scott JAG, et al. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. Lancet Neurol 2008;7(2):145-150. doi:10.1016/S1474-4422(07)70331-9

13 Ascoli M, Ferlazzo E, Gasparini S, et al. Epidemiology and Outcomes of Status Epilepticus. Int J Gen Med 2021;14:2965-2973. doi:10.2147/IJGM.S295855

14 Leitinger M, Trinka E, Giovannini G, et al. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. Epilepsia 2019;60(1):53-62. doi:10.1111/epi.14607

15 Kantanen AM, Sairanen J, Kälviäinen R. Incidence of the different stages of status epilepticus in Eastern Finland: a population-based study. Epilepsy Behav 2019;101(Pt B):106413. doi:10.1016/j.yebeh.2019.07.014

16 Kantanen AM, Reinikainen M, Parviainen I, Kälviäinen R. Long-term outcome of refractory status epilepticus in adults: a retrospective population-based study. Epilepsy Res 2017;133:13-21. doi:10.1016/j.eplepsyres.2017.03.009

17 Kantanen AM, Reinikainen M, Parviainen I, et al. Incidence and mortality of super-refractory status epilepticus in adults. Epilepsy Behav 2015;49:131-134. doi:10.1016/j.yebeh.2015.04.065

18 Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20(3):476-483. doi:10.1007/s12028-013-9935-x

19 Schubert-Bast S, Zöllner JP, Ansorge S, et al. Burden and epidemiology of status epilepticus in infants, children, and adolescents: A population-based study on German health insurance data. Epilepsia 2019;60(5):911-920. doi:10.1111/epi.14729

20 Rubinos C, Ruland S. Neurologic complications in the intensive care unit. Curr Neurol Neurosci Rep 2016;16(6):57. doi:10.1007/s11910-016-0651-8

21 DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. Epilepsia 1992;33 Suppl 4:S15-25. doi:10.1111/j.1528-1157.1992.tb06223.x

22 Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 1996;47(1):83-89. doi:10.1212/wnl.47.1.83

23 Kurtz P, Gaspard N, Wahl AS, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med 2014;40(2):228-234. doi:10.1007/s00134-013-3149-8

24 Hill CE, Blank LJ, Thibault D, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. Neurology 2019;92(1):e9-e18. doi:10.1212/WNL.0000000000006689

25 Rudin D, Grize L, Schindler C, et al. High prevalence of nonconvulsive and subtle status epilepticus in an ICU of a tertiary care center: a three-year observational cohort study. Epilepsy Res 2011;96(1-2):140-150. doi:10.1016/j.eplepsyres.2011.05.018

26 Laccheo I, Sonmezturk H, Bhatt AB, et al. Non-convulsive status epilepticus and non-convulsive seizures in neurological ICU patients. Neurocrit Care 2015;22(2):202-211. doi:10.1007/s12028-014-0070-0

27 DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia 1998;39(8):833-840. doi:10.1111/j.1528-1157.1998.tb01177.x

28 Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology 2000;54(2):340-345. doi:10.1212/wnl.54.2.340

29 Alvarez V, Drislane FW, Westover MB, Dworetzky BA, Lee JW. Characteristics and role in outcome prediction of continuous EEG after status epilepticus: a prospective observational cohort. Epilepsia 2015;56(6):933-941. doi:10.1111/epi.12996

30 Misra UK, Kalita J. Seizures in encephalitis: predictors and outcome. Seizure 2009;18(8):583-587. doi:10.1016/j.seizure.2009.06.003

31 Claassen J, Jetté N, Chum F, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. Neurology 2007;69(13):1356-1365. doi:10.1212/01.wnl.0000281664.02615.6c

32 Dennis LJ, Claassen J, Hirsch LJ, et al. Nonconvulsive status epilepticus after subarachnoid hemorrhage. Neurosurgery 2002;51(5):1136-1143; discussion 1144. doi:10.1097/00006123-200211000-00006

33 Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62(10):1743-1748. doi:10.1212/01.wnl.0000125184.88797.62

34 Giovannini G, Monti G, Polisi MM, et al. A one-year prospective study of refractory status epilepticus in Modena, Italy. Epilepsy Behav 2015;49:141-145. doi:10.1016/j.yebeh.2015.05.022

35 Delaj L, Novy J, Ryvlin P, Marchi NA, Rossetti AO. Refractory and super-refractory status epilepticus in adults: a 9-year cohort study. Acta Neurol Scand 2017;135(1):92-99. doi:10.1111/ane.12605

36 Mameniškienė R, Wolf P. Epilepsia partialis continua: a review. Seizure 2017;44:74-80. doi:10.1016/j.seizure.2016.10.010

37 Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53 Suppl 4:127-138. doi:10.1111/j.1528-1167.2012.03622.x

38 Ferlisi M, Hocker S, Trinka E, Shorvon S, International Steering Committee of the StEp Audit. Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: results from a global audit. Epilepsia 2018;59 Suppl 2:100-107. doi:10.1111/epi.14496

39 Rubinos C, San-Juan D, Alva-Diaz C, et al. Epilepsy care in Latin America and the Caribbean: overcoming challenges and embracing opportunities [published online March 27, 2024]. Semin Neurol. doi:10.1055/s-0044-1782616

40 Rubinos C, Reynolds AS, Claassen J. The ictal-interictal continuum: to treat or not to treat (and how)? Neurocrit Care 2018;29(1):3-8. doi:10.1007/s12028-017-0477-5

41 Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol 2021;38:1-29. doi:10.1097/WNP.0000000000000806

42 Woodruff BK, Britton JW, Tigaran S, et al. Cardiac troponin levels following monitored epileptic seizures. Neurology 2003;60(10):1690-1692. doi:10.1212/01.wnl.0000065881.46964.4f

43 Chin PS, Branch KR, Becker KJ. Postictal neurogenic stunned myocardium. Neurology 2005;64(11):1977-1978. doi:10.1212/01.WNL.0000163858.77494.7A

44 Rubinos C, Bruzzone MJ, Blodgett C, et al. Association of serum pyridoxal phosphate levels with established status epilepticus. Neurocrit Care 2023;38(1):41-51. doi:10.1007/s12028-022-01579-z

45 Cianfoni A, Caulo M, Cerase A, et al. Seizure-induced brain lesions: a wide spectrum of variably reversible MRI abnormalities. Eur J Radiol 2013;82(11):1964-1972. doi:10.1016/j.ejrad.2013.05.020

46 Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. Clin Neurophysiol 2007;118(8):1660-1670. doi:10.1016/j.clinph.2006.11.312

47 Leitinger M, Gaspard N, Hirsch LJ, et al. Diagnosing nonconvulsive status epilepticus: Defining electroencephalographic and clinical response to diagnostic intravenous antiseizure medication trials. Epilepsia 2023;64(9):2351-2360. doi:10.1111/epi.17694

48 Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591-600. doi:10.1056/NEJMoa1107494

49 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(9):631-637. doi:10.1056/NEJMoa002141

50 Gaínza-Lein M, Sánchez Fernández I, Jackson M, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurol 2018;75(4):410-418. doi:10.1001/jamaneurol.2017.4382

51 Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983;249(11):1452-1454.

52 Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339(12):792-798. doi:10.1056/NEJM199809173391202

53 US Food and Drug Administration. Ativan (lorazepam) injection. Accessed March 14, 2024. accessdata.fda.gov/drugsatfda_docs/label/2006/018140s028lbl.pdf

54 Sathe AG, Underwood E, Coles LD, et al. Patterns of benzodiazepine underdosing in the Established Status Epilepticus Treatment Trial. Epilepsia 2021;62(3):795-806. doi:10.1111/epi.16825

55 Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15(1):47-55. doi:10.1016/S1474-4422(15)00296-3

56 Dalziel SR, Borland ML, Furyk J, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet 2019;393(10186):2135-2145. doi:10.1016/S0140-6736(19)30722-6

57 Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393(10186):2125-2134. doi:10.1016/S0140-6736(19)30724-X

58 Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr 2016;16(1):48-61. doi:10.5698/1535-7597-16.1.48

59 Brigo F, Del Giovane C, Nardone R. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis. Epilepsy Behav 2019;101(Pt B). doi:10.1016/j.yebeh.2019.106466

60 Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135(Pt 8):2314-2328. doi:10.1093/brain/aws091

61 Chiu WT, Campozano V, Schiefecker A, et al. Management of Refractory Status Epilepticus. Neurology 2022;99(11):e1191-e1201. doi:10.1212/WNL.0000000000200818

62 Orser BA, Bertlik M, Wang LY, MacDonald JF. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 1995;116(2):1761-1768. doi:10.1111/j.1476-5381.1995.tb16660.x

63 Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al. Ketamine to treat super-refractory status epilepticus. Neurology 2020;95(16):e2286-e2294. doi:10.1212/WNL.0000000000010611

64 Zeiler FA, Teitelbaum J, Gillman LM, West M. NMDA antagonists for refractory seizures. Neurocrit Care 2014;20(3):502-513. doi:10.1007/s12028-013-9939-6

65 Buratti S, Giacheri E, Palmieri A, et al. Ketamine as advanced second-line treatment in benzodiazepine-refractory convulsive status epilepticus in children. Epilepsia 2023;64(4): 797-810. doi:10.1111/epi.17550

66 Pugin D, Foreman B, De Marchis GM, et al. Is pentobarbital safe and efficacious in the treatment of super-refractory status epilepticus: a cohort study. Crit Care 2014;18(3):R103. doi:10.1186/cc13883

67 Madžar D, Reindl C, Giede-Jeppe A, et al. Impact of timing of continuous intravenous anesthetic drug treatment on outcome in refractory status epilepticus. Crit Care 2018;22(1):317. doi:10.1186/s13054-018-2235-2

68 Fernandez A, Lantigua H, Lesch C, et al. High-dose midazolam infusion for refractory status epilepticus. Neurology 2014;82(4):359-365. doi:10.1212/WNL.0000000000000054

69 Muhlhofer WG, Layfield S, Lowenstein D, et al. Duration of therapeutic coma and outcome of refractory status epilepticus. Epilepsia 2019; 60(5):921-934. doi:10.1111/epi.14706

70 Marinus Pharmaceuticals. A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intravenous ganaxolone in status epilepticus (NCT04391569). Updated February 23, 2023. Accessed April 4, 2024. clinicaltrials.gov/study/NCT04391569

71 Liu A, Pang T, Herman S, Pascual-Leone A, Rotenberg A. Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit. Seizure 2013;22(10):893-896. doi:10.1016/j.seizure.2013.06.014

72 Dibué-Adjei M, Brigo F, Yamamoto T, Vonck K, Trinka E. Vagus nerve stimulation in refractory and super-refractory status epilepticus - A systematic review. Brain Stimul 2019;12(5): 1101-1110. doi:10.1016/j.brs.2019.05.011

73 Ng MC, El-Alawi H, Toutant D, et al. A pilot study of high-definition transcranial direct current stimulation in refractory status epilepticus: the SURESTEP trial. Neurotherapeutics 2023;20(1): 181-194. doi:10.1007/s13311-022-01317-5

74 Sage therapeutics reports top-line results from phase 3 STATUS trial of brexanolone in super-refractory status epilepticus. Sage Therapeutics. Published September 12, 2017. Accessed March 15, 2024. investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-reports-top-line-results-phase-3-status-trial

75 Vaitkevicius H, Ramsay RE, Swisher CB, et al. Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial. Epilepsia 2022;63(9):2381-2391. doi:10.1111/epi.17343

76 Jha R, Blitz SE, Chua MMJ, et al. Surgical management of status epilepticus: A systematic review. Epilepsia Open Published online March 8, 2024. doi:10.1002/epi4.12924

77 Legriel S, Lemiale V, Schenck M, et al. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med 2016;375(25): 2457-2467. doi:10.1056/NEJMoa1608193

78 Alkhachroum A, Der-Nigoghossian CA, Rubinos C, Claassen J. Markers in status epilepticus prognosis. J Clin Neurophysiol 2020;37(5): 422-428. doi:10.1097/WNP.0000000000000761

79 Baumann SM, De Stefano P, Kliem PSC, et al. Sex-related differences in adult patients with status epilepticus: a seven-year two-center observation. Crit Care 2023;27(1):308. doi:10.1186/s13054-023-04592-6